OBSERVATIONS ON BLOOD GAS TENSIONS AND ACID-BASE STATUS IN RESPIRATORY ILLNESSES IN INFANTS AND CHILDREN

by

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NOTE OF PREVIOUS PUBLICATIONS

Some results of this study have been published previously:

1. "Arterial Blood-gas Tensions and pH in Acute Lower Respiratory Tract Infections in Infancy and Childhood".
   Simpson, H. and Flenley, D.C. (1967), Lancet 1, 7.

2. "Oxygen Concentrations in Tents and Incubators in Paediatric Practice".
   Simpson, H. and Russell, D.J. (1967), Brit. med. J. 4, 201.

3. "Arterial Blood-gas Tensions and pH in Acute Asthma in Childhood".
   Simpson, H., Forfar, J.O., and Grubb, D.J. (1968)
   Brit. med. J. 3, 460.

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SUMMARY

The causes of death of 550 infants and children dying in hospital over a ten year period were analysed as a prelude to the main study. Serial measurements of blood gas tensions and pH were made in 50 children with acute lower respiratory tract infections, 21 with acute asthma, 25 with cystic fibrosis, and 23 newly born infants in the first hour of life. Arterial blood lactate and pyruvate concentrations were measured in 35 children with acute or chronic hypoxaemia. The effects of treatment, particularly oxygen and alkali therapy on these variables were investigated. Measurements were also made of the concentrations of oxygen attainable in tents and incubators, tested under ideal, and routine working conditions.

The analysis of deaths shows that respiratory disorders, particularly pneumonia, account for approximately 25 per cent of 'medical' deaths in hospital. The main conclusions, in answer to the questions posed in Section I, p. 7, are enumerated:

1. Hypoxaemia, an increase in carbon dioxide retention and metabolic acidosis are commonly present in acute lower respiratory tract infections and severe acute asthma. In cystic fibrosis, an increase in Pco_2, often well compensated, occurs only in the late stages of the disease.

2. Clinical signs are unreliable as estimates of Po_2, Pco_2 and pH in acute respiratory illnesses. In cystic fibrosis there is a good relation between the clinical 'grade' in groups of patients and arterial oxygen tension. There are, however, no reliable methods of predicting blood gas tensions in individual patients.

3. Metabolic acidosis in acute respiratory disorders is due, at least in part, to the accumulation of lactic acid. Measurements of blood lactate and lactate/pyruvate ratio as indices of hypoxia are of limited value in routine clinical practice.

4. In acute lower respiratory tract infections and acute asthma hypoxaemia is not invariably relieved by the administration of 40 per cent oxygen. There appears to be no danger of producing CO_2 narcosis with oxygen in acute respiratory infections. During exacerbations of infection in cystic fibrosis and in severe asthma with ventilatory failure, however, oxygen is potentially hazardous.

5. The administration of sodium bicarbonate is of value in the treatment of severe respiratory failure in asthma, and is an important adjunct to intermittent positive pressure respiration (IPPR) in the management of asphyxiated newly born infants.

6. In acute respiratory infections in infancy a Pco_2 above 65 mm Hg and pH below 7.20 are of grave prognostic significance in the absence of prompt treatment. In cystic fibrosis sustained hypercapnia is usually a terminal occurrence.

7. Therapeutic concentrations of oxygen in tents are often difficult to maintain in routine practice.

INTRODUCTION

I first encountered the problems of management of acute respiratory illness in children as a House Physician at the Royal Hospital for Sick Children, Edinburgh, in 1962. No objective means of assessing respiratory function were available in the hospital at that time; even so, most patients with respiratory disorders seemed to respond to treatment and recover uneventfully. The unexpected death of a child with asthma a year later convinced me that clinical judgement was not always reliable, and indeed could be misleading. There was a clear need to combine a high standard of clinical skill with more objective methods of assessment.

In a lecture to the Royal College of Physicians of Edinburgh, Christie, (1964) emphasised the significance of respiratory insufficiency in certain acute disorders in adults, and the need for measurements of arterial blood gas tensions and pH to help guide therapy. The possible application of these methods to children was apparent, and I resolved to investigate the importance of hypoxaemia and acid-base disturbance in infants and children admitted to hospital with respiratory illnesses.

Many excellent articles and books had been written by that time on hypoxaemia, and the principles underlying oxygen therapy,(Haldane, 1917; Barcroft, 1920; Meakins and Davies, 1925; Barach, 1948; Comroe and Dripps, 1950; Knowles, 1959; Bates and Christie, 1964). Despite the wealth of information available, however, objective measurements as criteria of oxygen therapy were not widely used in clinical practice. The application of existing knowledge and further clinical research in this field since 1960 has largely resulted from the introduction of

accurate blood gas electrodes suitable for routine use. In December 1965, equipment for blood gas analysis became available, which made possible most of the observations presented in this thesis.

As a prelude to the studies undertaken, I analysed the main causes of death of infants and children who died in the general medical wards of the Royal Hospital for Sick Children, Edinburgh, during the preceding ten years, in an attempt to estimate the possible importance of respiratory failure as a primary or contributory cause of death.

Children with acute respiratory infections, severe acute asthma, cystic fibrosis and congenital cyanotic heart disease were then studied in Edinburgh between January 1966 and June 1968. Investigations in asphyxiated newly born infants were carried out in San Francisco between July 1968 and June 1969.

The material in this thesis is presented in seven sections, the first three of which are subdivided into two chapters. In Section I the causes of death of infants and children in hospital are analysed, and a description given of the clinical and laboratory methods employed in subsequent studies. The investigations carried out and the results obtained in each of the respiratory disorders studied are described in Sections II to VI. Finally, in Section VII, an evaluation of methods of administering oxygen is reported. The format of each chapter or section is that of a conventional publication, with an introductory paragraph and a description of the patients, followed by results, discussion and a summary of the main conclusions.

S E C T I O N I

Chapter 1

ANALYSIS OF CAUSES OF DEATH OF CHILDREN DYING IN HOSPITAL

CAUSES OF DEATH OF INFANTS AND CHILDREN

An analysis was made of the main causes of death of 550 infants and children who died in the Royal Hospital for Sick Children, Edinburgh, between 1 January 1957 and 31 December 1966, to determine the proportion of deaths due to conditions which may have been associated with acute cardio-respiratory failure. A report of this nature, concerned only with mortality and not morbidity underestimates the real size of the clinical problem and the total number of patients who require the special facilities outlined by Christie (1963) for adults, and by Jones (1966) for infants and children.

Method

The name, age, diagnosis and date of death of each child who died in Wards 1, 2 and 5 (the medical wards, the Royal Hospital for Sick Children, Edinburgh) during the ten-year period 1957 to 1966 were obtained from ward record statistics. Death certificates were not checked so that it is not certain that the cause of death listed invariably corresponded to that given on the death certificate. The main causes of death were classified without reference to individual case records. An analysis of the deaths of infants and children in whom cardio-respiratory failure may have played a part was then made based on a scrutiny of individual case records and autopsy reports.

Results

General Analysis:

An analysis of the number of admissions, deaths and ages at death of 550 children in the series is presented in Table I. The number of deaths occurring each year is fairly constant despite a 30 per cent

increase in the number of children admitted annually over the ten-year period. The vast majority of deaths occur in pre-school children, particularly in the first year of life. Table 1a shows the seasonal distribution of these deaths, the peak quarter being January to March and the smallest number occurring in July to September. The proportion of deaths due to pneumonia and heart disease each year is fairly constant at approximately 35 per cent of all deaths (Table 1b).

Table 2 shows the main causes of death. More than forty per cent were due to cardio-respiratory diseases. Potentially remediable disorders such as septicaemia, meningitis, hypothermia and prematurity constitute a further 12 per cent. In Tables 2a, 2b and 2c these deaths are further classified according to the age of occurrence. The causes of death and trends shown with age reflect in a general way the national statistics (see Registrar General data, 1962-65). Respiratory disorders are shown in Table 3. By far the largest number were due to acute respiratory tract infection, mainly pneumonia. There was only one death from asthma despite the enormous clinical problem presented by children with severe acute asthma.

Specific Analysis:

A detailed analysis based on scrutiny of case records was made of those groups shown on Table 4. These are the deaths where cardio-respiratory failure may have been of importance. The number of records available in each group was far fewer than the actual number of recorded cases.

Congenital Heart Disease

An analysis of the case records of 72 infants who died of congenital heart disease is shown on Table 5. Most were under one year old and

death occurred most often on the first day of admission to hospital. Only five cases had been investigated prior to their demise. The findings at autopsy in 62 infants suggest that many of the cardiac abnormalities would have been amenable to surgical treatment. Seventeen infants had additional congenital abnormalities. Pneumonia and atelectasis were associated causes of death in over one third of the cases.

Acute Respiratory Tract Infection

Of the 50 infants with pneumonia, six had proven staphylococcal pneumonia. Table 6 is an analysis of the remaining 44 cases of bronchopneumonia. The majority of the infants who died were under one year of age, and death occurred most often on the day of admission to hospital. Twenty-five infants had no associated defects, but 19 (43 per cent) had congenital abnormalities which may have been a contributory cause of death - a proportion similar to that found by Gardner et al. (1967) in their analysis of deaths associated with respiratory tract infection in childhood. Ten infants were hypothermic.

The six infants with staphylococcal pneumonia were under three months of age, and none had associated congenital abnormalities. Of the eight children dying of upper airway obstruction, three had died on the way into hospital or directly on arrival (these cases were nevertheless coded on the ward coding system). Except for one patient with nephrocalcinosis no abnormalities were detected in the remaining five. In the entire respiratory group there was no correlation between the duration of illness prior to admission to hospital and the duration of stay in hospital before death.

Infections

Only 14 of 29 case records of patients who died of septicaemia were available. The records analysed were not representative of the entire group as the missing case records were of infants who died of E. coli septicaemia. Eleven of the 14 cases were under one year of age. The meningococcus was the causative organism in eight patients, staphylococcus pyogenes in two, and haemolytic streptococcus in a further two. In three infants pneumonia was an associated cause of death. Autopsy was carried out on all of these patients and no underlying congenital abnormalities were detected.

Hypothermia

The case records of 15 infants in whom the primary cause of death was hypothermia were examined. Their ages ranged from two days to ten weeks; 11 were under one month of age. The majority had been ill for less than a day before admission to hospital, and 11 had died within 48 hours of admission. Pneumonia was the associated cause of death in six of these infants and pulmonary haemorrhage in a further four. Only one had an underlying congenital abnormality (congenital neuroblastoma diagnosed at autopsy).

Miscellaneous

"Prematurity" - these four infants died in the first week of life of associated respiratory complications. None had underlying abnormalities at autopsy.

Summary

A general analysis of the causes of death of 550 children dying in the Royal Hospital for Sick Children, Edinburgh, between 1957 and 1966 is presented. Cardio-respiratory problems accounted for more than forty per cent of all deaths.

A more detailed analysis of deaths due to congenital heart disease, acute respiratory infections, septicaemia, hypothermia and "prematurity" suggests that an appreciable number of otherwise healthy infants and young children die soon after admission to hospital from conditions which may be regarded as 'potentially reversible'. A high proportion of these infants have no associated abnormality. As many case records were not available for examination it is likely that the problem is even greater than the data presented suggest. An assessment of the importance of hypoxaemia, acid base disturbance and oxygen therapy in children suffering from respiratory illnesses which may cause death in hospital is the main objective of the studies outlined in subsequent chapters of this thesis.

S E C T I O N I

Chapter 2

METHODS

METHODS

Organisation and Background

The studies in pneumonia, asthma and cystic fibrosis were carried out at the Royal Hospital for Sick Children, Edinburgh, between 1965 and 1968, and predated the provision of a blood gas service there. Most of the patients were encountered during the course of my routine clinical duties, and the various studies were undertaken whenever time permitted. Initially all clinical assessments, blood sampling and blood gas analysis were performed without assistance; a research nurse and a technician were appointed later to help in the study of patients with cystic fibrosis. Facilites for the measurement of blood lactate and pyruvate were provided in 1967 in the Department of Medicine, Royal Infirmary, Edinburgh, by kind permission of Professor K W Donald. These measurements were made only in children admitted latterly to the various clinical groups.

Studies in the newly born infant were carried out in the Newborn Nursery and delivery room at the Moffat Hospital, University of California Medical Centre, San Francisco, between June 1968 and June 1969, under the direction of Dr W H Tooley. They were conducted by a team which included three or four doctors, a technician, and specially trained nursing staff. The personnel involved were also responsible for follow-up care.

Patients - Plan of Investigation

The study comprised initially fifty patients with acute lower respiratory tract infection, twenty-one with severe acute asthma and twenty-five with cystic fibrosis. A further nine patients with these conditions, and nine with cyanotic heart disease were admitted later

to the study of lactate and pyruvate metabolism. Twenty-three newly born infants were also investigated.

The consultant under whose care these patients were admitted was responsible for their clinical management; in many cases, however, I was fortunate to be closely concerned with routine care, and decisions on treatment. In each of the groups of patients studied attempts were made to answer some of the following questions:

The actual levels of Po_2, Pco_2 and pH?

The value of clinical signs as estimates of Po_2, Pco_2 and pH?

The mechanisms of hypoxia and acidosis?

The importance of oxygen therapy?

The role of buffers and/or assisted ventilation?

The value of blood gas measurements in guiding treatment and indicating prognosis?

No single study was designed to answer all of these questions; even so, discussion of them is often possible from the results obtained. Clinical details of patients, the criteria for their selection, and the plan of investigation in each of the clinical conditions studied are described fully in the appropriate sections.

As most of the patients studied suffered from severe acute illnesses demanding immediate action, parental consent was often not requested before blood samples were taken; in less urgent situations it was always obtained.

PROCEDURES AND MEASUREMENTS

Sampling of arterial or arterialised capillary blood

Arterial blood was taken from the brachial (Reynolds, 1963a) radial (Bucci et al., 1966) or femoral artery in all patients outwith the

newborn period. In newly born infants umbilical blood samples were obtained using the methods described by Kitterman et al. (1970). Heparinised capillary blood was obtained from the warmed heel or ear lobe.

Measurement of inspired oxygen concentration

Patients were studied breathing air or oxygen-enriched air. During the early part of the study inspired gas samples were obtained as described by Simpson and Flenley (1967), Simpson, Forfar and Grubb (1968). A brief description of these methods is given in the relevant sections. Later it was possible to study patients at one constant inspired oxygen concentration ($\pm$ 0.5%) using the high-flow system described by McKenzie (1965) in conjunction with a perspex head tent. A similar system based on mixing air and oxygen in desired proportions was used in studying newborn infants. Provided the flow remained above 8-10 litres per minute a constant inspired oxygen concentration ($\pm$ 0.5%) was achieved. The oxygen concentration of gas samples was determined by a DCL 101 paramagnetic oxygen analyser calibrated with air and nitrogen (Nunn, 1964). A Beckman oxygen analyser was used in the newborn studies.

Measurement of lower aortic blood pressure

All newly born infants were nursed in radiantly warmed cribs. Catheters were inserted into the abdominal aorta through an umbilical artery; in one infant the catheter was placed in the umbilical vein with its tip in the left atrium. Aortic blood pressure was measured directly as described by Kitterman et al. (1969). The umbilical

catheters were also used to infuse fluid and electrolytes, and alkali for the correction of metabolic acidosis. Blood or albumen was also given to correct severe hypotension.

Measurement of heart rate, respiratory rate and minute volume

Heart rate was monitored continuously in all newly born infants. Respiratory rate and minute ventilation were measured in four cases, and maintained constant throughout the period of study in one. Recordings were made on a polygraph (Grass Instruments Co., Quincy, Mass.). Ventilation was measured with a pneumotachograph, the output of which was integrated electronically to obtain tidal volume. The pneumotachograph was calibrated with a gas mixture of the same temperature and composition as the gas inspired during the study. Heart rate was counted from ECG or arterial blood pressure recordings.

LABORATORY METHODS

Measurement of blood gas tensions and pH

Arterial or arterialised capillary blood samples were analysed at 37°C for Po_2, Pco_2 and pH immediately or at latest within fifteen minutes. All measurements were performed in duplicate. The values obtained in each case were corrected for the patient's temperature, using the data of Kelman and Nunn (1966) or the blood gas calculator of Severinghaus (1966).

Oxygen tension (Po_2), determined in arterial samples only, was always measured first with a Radiometer (Clark type) Po_2 electrode (type E5044 or E5046) which had previously been calibrated with tonometered blood by the method of Flenley et al. (1967). It was calibrated with room air before and after each determination. The meter was set to

zero daily with nitrogen. Duplicate measurements had to agree to within 2 mm Hg.

Arterial blood carbon dioxide tension (Pco_2) was measured with the Severinghaus electrode (type E5030 or E5036), the calibrating gases having been analysed previously with Haldane apparatus to within $\pm$ 0.02%. The Pco_2 of capillary samples was measured with the Severinghaus electrode (type E5036) or by the interpolation method (Siggaard-Andersen et al., 1960) using the Radiometer G297/G2 glass electrode and PHM22 or PHM27 meter. During routine use the Astrup technique was compared with the Severinghaus electrode on 91 occasions. There was a linear relationship between the interpolation Pco_2 determination and the Severinghaus electrode Pco_2 measurements with one standard deviation of 2.5 mm Hg about the regression line.

Arterial and capillary blood pH was measured with the G297/G2 electrode and PHM22 or PHM27 meter. Each experimental determination for pH was bracketed with the reading of a standard buffer solution (Radiometer Precision Buffers 6.840 and 7.381). Then after adjusting the value for changes in calibration a correction factor was made when the elapsed time exceeded five minutes (Severinghaus et al., 1956). The pH was expressed to the nearest 0.01 pH units as the precision buffers are only accurate to $\pm$ 0.005 pH units. Duplicate readings in blood were within 0.004 pH units.

Measurement of haemoglobin

The haemoglobin concentration (G/100 ml) was determined using an EEL haemoglobinometer.

Measurement of haematocrit

The haematocrit was determined by spinning blood in heparinised capillary tubes at 7500 RPM for ten minutes.

Calculations

Oxygen saturation (So_2) was calculated using the Severinghaus (1966) blood gas calculator for all cases. No correction was made in infants under the age of three months for the presence of foetal haemoglobin as the relative proportions of adult and foetal haemoglobin were not known in these cases. The alveolar air equation (Comroe et al., 1962) was used to calculate the alveolar oxygen tension (PAo_2) assuming a respiratory exchange ratio of 0.8. The alveolar oxygen tension difference ($A\text{-}aDo_2$) was then obtained by subtraction. Base excess values were derived from the nomogram of Siggaard-Andersen (1963) and related to the patient's actual haemoglobin level. A correction factor was made for the *in vivo* effect of Pco_2 (see Appendix 1).

Measurement of arterial blood lactate and pyruvate

Measurements were made from one 5 ml blood sample. The arterial blood was sampled from the patient into a cold heparinised glass syringe. 4.5 ml of blood was immediately transferred into a chilled glass tube, the remaining 0.5 ml being retained for blood gas analysis. 4 ml were then pipetted using a cold pipette into a test-tube containing 4 ml 5% perchloric acid. The tube was stoppered, shaken vigorously and refrigerated. It was later centrifuged and the supernatant recentrifuged. This fluid was then used for analysis of lactate and pyruvate by the respective Boehringer (1962) enzymatic methods which are based on the conversion of NAD or NADH, measured in an ultraviolet light spectrophotometer at 340 mu.

The normal range of blood lactate values by this method is 0.48-1.74 mM, and of pyruvate 0.055-0.085 mM.

Measurement of serum transaminases (SGPT, SGOT)

Serum transaminases were measured in the routine biochemistry laboratory, the levels obtained being expressed in Sigma-Frankel Units/ml.

The normal (adult) blood serum concentration activity of these enzymes is 5-40 units/ml. Higher values are obtained normally during the early months of life GOT < 120 units/ml; GPT < 90 units/ml.

Measurement of electrolytes

Serum sodium, potassium and chloride concentrations were measured in the routine biochemistry laboratory by standard flame photometric methods.

COMMENTS ON METHODS - SOURCES OF ERROR

Arterial and capillary blood sampling

It was exceedingly difficult to sample blood from young infants without disturbing them. The problem was often simpler in older children, provided their confidence was won in advance and several minutes were allowed to elapse between the injection of local anaesthetic and actual arterial puncture. In ill patients with carbon dioxide retention arterial puncture was well tolerated, and often as easily performed as venepuncture. Hyperventilation or crying at the time of puncture may have produced a fall in Pco_2, and have 'masked' the true incidence of ventilatory failure in the patients studied. Owing to the shape of the oxygen haemoglobin dissociation curve, however, Po_2 would not have been affected to the same extent as Pco_2 (Comroe et al., 1962). These

problems did not apply in the newborn infant studies where blood samples were obtained without disturbance.

Arterial samples were preferred to capillary samples in newly born infants (Gandy et al., 1964) and in older infants and children when precise information was required, and whenever sampling from the warmed extremity was difficult on account of "shock" or localised peripheral stasis. Figure I shows the results of a comparison of arterial and warmed heel capillary blood pH in twenty patients in whom the conditions of capillary blood flow was noted. In each case the heel had been immersed in warm water for several minutes before sampling. The lack of agreement between these methods when peripheral stasis was present influenced the decision to rely on arterial samples for accuracy. The Po_2 measurements reported were all made in arterial blood samples, though several authors (Stamm, 1967; Matthews et al., 1969) have noted the good correlation between arterial and arterialised capillary Po_2 when sampling conditions are optimal.

Presentation of acid-base variables

The pH notation has been criticised (Schwartz and Relman, 1961; Huckabee, 1961; Campbell, 1962; Owen et al., 1965; Lennon and Lemann, 1966; Nelson and Reigal, 1969; Flenley, 1971) and defended (Hills and Reid, 1965; Davis, 1967; Kildeberg and Engel, 1969). Filley (1969) traces the beginnings of the so-called "Great Transatlantic Acid-Base Debate" (Bunker, 1965) between the continental and Anglo-American schools of acid-base physiology and describes the differences in their approach. The disagreements are not on the fundamental measurements, pH, Pco_2 and Po_2, but on derived measurements, plasma bicarbonate (Hco_3^-) and "base excess" which are convenient under certain circumstances as estimates of the "metabolic component" of an acid-base

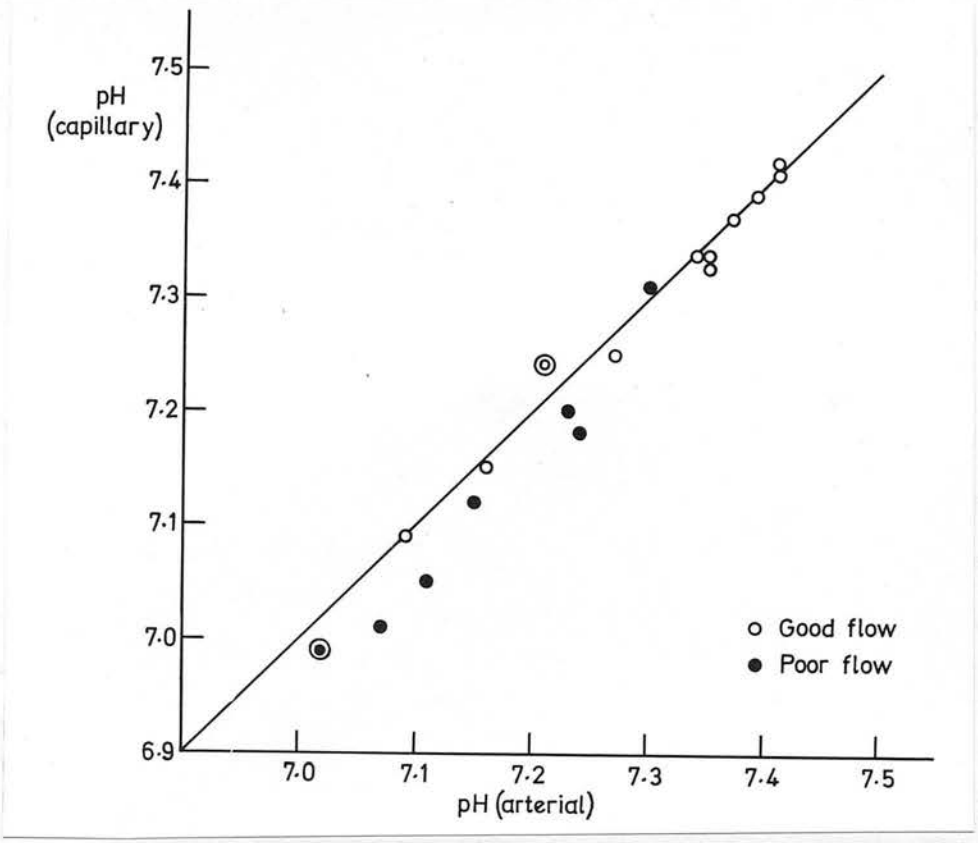

Figure 1

Paired arterial and arterialised capillary pH results in relation to the line of identity. The differences are greatest with peripheral circulatory failure and poor capillary blood flow.

disturbance. Provided the limitations of this approach are appreciated as many authors, including Singer and Hastings (1948) and Sigaard-Andersen (1964) have warned, it is extremely useful clinically and has been adopted here. "Base excess", which relates to whole blood and not plasma alone, is preferred to plasma bicarbonate (Hco_3^-) as an index of alkali reserve. These factors which may affect the derived value "base excess" and have nothing to do with a true and treatable accumulation of acid anions are discussed by Nelson and Riegel (1969).

Definition of lactic acidosis

The problem of defining lactic acidosis has been discussed by Oliva (1970) and there is still lack of uniform agreement to what is meant by this term. He defines lactic acidosis as a blood lactate concentration greater than 2.0 mEq/litre in association with an arterial pH below 7.37 in the absence of other causes of acidosis. This definition is accepted here, recognising that a lactate level of 2.0 mEq/litre is somewhat higher than the upper limit of the normal values obtained using the enzymatic analytical method when blood samples are obtained under resting steady state conditions. It seems reasonable to accept the higher level in view of the non-steady-state sampling condition of acutely ill children who had not been deliberately fasted in the preceding twelve hours. Similarly, blood pyruvate concentrations may be higher than would have been obtained had sampling conditions been ideal. The extent to which the values presented deviate from steady-state values in fasting subjects at rest is not known.

SECTION II

Chapter 1

BRONCHIOLITIS AND BRONCHOPNEUMONIA

BRONCHIOLITIS AND PNEUMONIA

INTRODUCTION

In Britain bronchiolitis and bronchopneumonia are the main respiratory illnesses causing hospital admission of infants under the age of two years. The former has been described as "an acute respiratory disorder of infants and young children, often occurring in epidemics and characterised by a preceding upper respiratory tract infection, followed by cough, shallow rapid respirations, and expiratory wheeze. Suprasternal and subcostal indrawing on inspiration occurs and the child shows evidence of emphysema" (Lang et al., 1964). In bronchopneumonia, on the other hand, overinflation of the chest is less evident clinically and pneumonic changes are prominent on chest X-rays. It is sometimes easy to distinguish these conditions, particularly during epidemics of bronchiolitis; at other times, however, clinical separation may be difficult or impossible. For this reason bronchiolitis and bronchopneumonia are often considered together as "bronchiolitis"(Heycock and Noble, 1956, 1962; Disney et al., 1960. These authors report a mortality rate of approximately five per cent for "bronchiolitis" which compares with 1-2 per cent in series where the diagnosis of bronchiolitis is made on stricter criteria (High, 1957; Elderkin et al., 1965). These deaths often occur shortly after admission to hospital and the precise cause is often in doubt.

The importance of hypoxaemia and the need for oxygen in these cases was emphasised by Morrison (1955), Reynolds (1963a), Varga and Zsuzsanna, H. (1966), and Downes et al. (1968). In their report of 32 cases of lower respiratory tract infection Simpson and Flenley (1967) stressed the

unreliability of clinical signs of hypoxaemia, the occasional need for an inspired oxygen concentration greater than 40 per cent to maintain a normal Po_2, and the grave prognostic importance of a pH below 7.20 and Pco_2 above 65 mm Hg. Here the clinical and blood gas findings in 45 cases of acute lower respiratory tract infection are correlated and the response to oxygen administration described. The series includes 26 cases previously described by Simpson and Flenley (1967) and excludes infants with acute laryngo-tracheo-bronchiolitis or proven staphylococcal pneumonia.

PATIENTS - PLAN OF INVESTIGATION

Patients

The 45 patients were admitted to the Royal Hospital for Sick Children between 1965 and 1968, mainly during the winter months. At the outset only severely ill cases were investigated. Selection was less strict later; even so, the clinical condition of each patient studied had caused concern and no mildly affected infant is included in the series. These infants are described in Table 7. There were 24 males and 21 females. Their ages ranged from two weeks to 35 months and all but five were under one year. Eight weighed less than 2.5 Kg at birth and 16 were 2 S.D. or more below average weight for age and sex on admission to hospital. Case 26 was the only patient who weighed more than 2 S.D. above the mean for age. A previous history of croup, bronchitis or bronchiolitis was obtained in 15 cases. The duration of symptoms was usually less than five days but was a week or more in seven cases. A history of antecedent or concurrent upper respiratory infection in an older sibling or an adult member within a family was often elicited. Respiratory distress and a dry repetitive cough preceded by a coryzal stage were

common presenting symptoms; cyanotic or apnoeic attacks, vomiting and diarrhoea were less frequent. Chest signs were generally bilateral with overinflation, indrawing of the intercostal spaces and widespread crepitations. Rhonchi were less common. Areas of consolidation, collapse of hypertranslucency were seen on chest X-rays. Antibiotics, usually penicillin, had been prescribed in 19 cases prior to admission. The clinical diagnosis of the consultant under whose care the patient was admitted is also shown for each case in Table 7. The fact that it was often different from the radiological diagnosis (see Table 10). emphasises the difficulties in diagnosis; no further attempt is made to separate bronchiolitis and pneumonia in this report.

Four infants were known to have congenital abnormalities (Cases 31, 32, 36 and 41). Werdnig-Hoffman disease had been previously confirmed in Cases 31 and 32. Case 36 had had a spina bifida repair soon after birth and a Pudenz valve inserted. Case 41 was a mongol child with a suspected ventricular septal defect. A diagnosis of paroxysmal atrial tachycardia was made in Case 37, with the Wolff-Parkinson-White pnenomenon on ECG. Case 42 was shown to have agammaglobulinaemia during the course of his illness. Cystic fibrosis of the pancreas was considered in the diagnosis in Cases 19, 22 and 28; the sweat sodium and chloride concentration was normal in each.

The laboratory findings in these patients are presented in Table 8. The haemoglobin was below 10 G% in seven patients, the lowest values obtained being 5.8 G% and 8.0 G% in Cases 36 and 45 respectively. The white cell count ranged from 4,000 to 44,200/cu mm. It was between 6,000 and 14,000/cu mm in 25 of 43 cases and exceeded 20,000/cu mm on five occasions. There was usually a preponderance of lymphocytes over polymorphs, irrespective of the total count.

Staph. pyogenes, pneumococci, coliforms and Staph. albus were the main organisms isolated from throat and nasal swabs. Blood cultures were positive in three of 25 patients, the infecting organism being klebsiella aerogenes (Case 23), Staph. pyogenes (Case 26) and E. coli (Case 37). Antibiotics had not been prescribed for these cases before admission. Despite the isolation of Staph. aureus from blood culture Case 26 is retained in this series as the clinical and radiological course of her illness was not characteristic of staphylococcal pneumonia. Pathogens were isolated from rectal swabs in three of the 45 patients. E. coli 0119 was isolated in Case 6, Shigella sonnei in Case 44, and E. coli 0127 in Case 45. Virology studies were not undertaken as the necessary diagnostic techniques were not then available in the City Hospital, Edinburgh.

Serum sodium, potassium and chloride and urea nitrogen levels were within normal limits in 11 of 14 patients. The serum sodium was above normal in Cases 19 (serum Na 162 mEq/litre) and 30 (serum Na 156 mEq/litre) and below normal in Case 36 (serum Na 128 mEq/litre). The BUN exceeded 50 mg % in these cases.

Lumbar punctures were carried out in 10 patients. In Case 36 30 cells/mm were seen in CSF but no growth was obtained on culture. CSF findings were within normal limits in the remaining cases.

Plan of Investigation

The infants were assessed clinically within 24 hours of admission to hospital and the signs of respiratory disease evaluated using the system shown in Table 9. Blood samples were obtained in a further 30 minutes while the patient breathed air or one constant oxygen concentration for at least 15 minutes, oxygen having been given initially on clinical

grounds without reference to blood gas data. At the time of sampling cyanosis was assessed as present or absent by two independent observers (H.S. and a nurse) viewing the patient in daylight or tungsten artificial lighting. All equivocal observations were classed as "cyanosis absent". Any restlessness and impairment of consciousness was also noted.

In Cases 1, 4-9, 27, 28, 33-42, heparinised capillary blood was obtained from the warmed heel but oxygen tension was not measured in these samples. In all other cases blood was taken in a heparinised syringe from the brachial or femoral artery (Reynolds, 1963a) and the site of sampling noted. No immediate sequelae other than minor haematomas resulted from these punctures. Inspired gas samples were taken from within one inch (2.5 cm) of the child's lips into 100 ml glass syringes. In patients 1, 2, 4, 7, 22, 27 and 30, the inspired oxygen concentration is the mean of the value in these two samples taken immediately before and after each blood sample. The maximum difference observed was four per cent. In Cases 16, 18, 19, 31, 37, 42-45, a constant inspired oxygen concentration ($\pm$ 0.5%) was maintained throughout the period of sampling. Subsequent blood and gas samples were taken as determined by the clinical progress.

Conventional therapy with humidified oxygen and antibiotics was always used and where indicated clinically anti-spasmodics, steroids and digoxin were given. The routine use of sedatives was avoided. Correction and maintenance of fluid and electrolyte balance was seldom possible without resorting to tube feeding or parenteral replacement. Infusion of sodium bicarbonate preceded initial investigation in Cases 16 and 17; in the remaining cases sodium bicarbonate was infused when the base excess exceeded -8 mEq/litre. Infusions were given over a period of

two to three minutes in a dose calculated as follows: weight (Kg) x base excess (mEq/litre) x extracellular fluid space (0.3). Intermittent positive pressure respiration (IPPR) was employed in the treatment of Cases 8, 30, 37 and 44.

RESULTS

Clinical and physiological observations were made on 45 infants with bronchiolitis or bronchopneumonia. Forty of these survived and five died (Cases 30, 36, 42, 44 and 45). A summary of the clinical courses of the illnesses of these five infants prior to death is given in Appendix 2. The two patients (Cases 31 and 32) with Werdnig-Hoffman disease survived, but died subsequently from further respiratory complications. Case 14 remained in hospital for investigation of chronic diarrhoea following clinical recovery from his respiratory infection.

Results are presented under four categories: initial clinical observations, blood gas tensions and pH on admission, the correlation of these and subsequent measurements with clinical observations, and the effects of the administration of oxygen.

Clinical Observations

The main clinical observations at the time of diagnosis are shown in Table 10. Seventeen of the 45 infants were too ill to be studied in air and were given oxygen from the outset.

Body Temperature

The initial temperature was less than 36°C in six cases. These infants were nursed in Isolette incubators and the body temperature was slowly raised by approximately 1°C every two hours. A temperature of 37-38°C was reached in all but one case (Case 45). The initial rectal temperature was above 39°C in four infants.

Restlessness

Fourteen infants were considered to be restless. They were irritable, cried a great deal and were not easily consoled by nursing attention or feeding. None had a recognised cause of pain such as otitis media or meningitis. The limb and head rolling movements described by Morrison (1955) were prominent in this group. Restlessness usually lessened when these infants were placed in oxygen.

Cyanosis

Fifteen infants were judged to be cyanosed. Of these, five were breathing oxygen. Conditions were not optimal for assessing cyanosis as most of the cases were studied in winter-time when artificial lighting was in use by day as well as at night.

"Unresponsiveness"

Fourteen patients were feeble, inactive and unresponsive to moderate stimulation, such as pinching the skin or pricking the sole of the foot. The skin colour of infants in this group was often pale or ashen. Cases 1, 19, 30, 37 and 45 were in a state of 'shock' with peripheral circulatory failure. The two infants with hypernatraemia (Cases 19 and 30) are included in this 'unresponsive' group, as are the only three patients in the series with an initial rectal temperature below 35^{o}C (Cases 1, 43 and 45). Unresponsiveness and restlessness were usually mutually exclusive signs; both were considered to be present in Case 8.

Respiratory Rate

The respiratory rate at the time of admission varied from 26 to 120 per minute in the 42 cases in whom it was recorded. The respiratory rate was 50 per minute or more in 25 cases, and under 40 per minute in five.

Heart Rate

During periods of quiet breathing the heart rate ranged from 150 to 170 per minute in most infants. Initial heart rate was 120 per minute or less in five infants, and 170 per minute or more in a further eight. Case 37 had associated paroxysmal tachycardia with a heart rate above 200 per minute.

Respiratory Score

The respiratory score was computed in 25 patients and varied from 1 to 7. It quickly became apparent that low scores were obtained not only in infants who were least ill clinically, but also in very sick infants in whom respiratory movements were feeble due to weakness or exhaustion.

Dehydration

The degree of dehydration present was assessed retrospectively by noting the percentage weight gain 48-72 hours later, following fluid and electrolyte replacement. Accurate records over this period of time were available for 30 patients. A weight gain exceeding 5 per cent of the initial admission weight occurred in Cases 1, 3, 17, 23, 25 and 28. None of these had been considered to be severely dehydrated on clinical grounds when examined initially, which suggests that the usual indices of dehydration (sunken eyes and fontanelle, dry mucous membranes, inelastic skin) reflect only the most severe degrees of fluid depletion, and that significant dehydration may be less easily detectable clinically. "Dehydration" is not shown as a separate column in Table 10.

Chest X-rays

In all cases P-A chest X-rays were taken soon after admission to hospital. These were interpreted and categorised into three main groups by one radiologist (G.R.S.) without reference to the clinical or blood gas findings:

Segmental pneumonia - consolidation of a segment of a lobe

Lobar pneumonia - consolidation of one or more lobes

Bronchopneumonia - widespread patchy consolidation in one or both lungs

Separation was not always clear cut, and some X-rays in each category also showed small areas of atelectasis. The X-rays were further divided into those with and those without hyperinflation of the lungs.

Pneumonic changes were evident in 44 cases and associated with hyperinflation of the lung fields in 27. Case 15 showed hyperinflation only. A radiological diagnosis of bronchopneumonia was made in 20 patients, segmental pneumonia in a further 16 and lobar pneumonia in eight.

Blood Gas Tensions and pH on Admission

Measurements and calculated data on admission to hospital are shown in Table 11. Hypoxaemia was common, the Po_2 being below 80 mm Hg in 18 of the 31 cases in whom it was measured, and below 50 mm Hg in 10. Carbon dioxide retention with a Pco_2 over 50 mm Hg was present in 19 cases, but in five the Pco_2 was below 30 mm Hg. The pH ranged from 7.09 to 7.46 and was below normal in 27 cases. The arterial oxygen saturation ranged from 44.8 to 100 per cent and was below 90 per cent in 13 patients. The alveolar arterial oxygen tension differences were above normal in all but two cases (Cases 24 and 40). Base excess values ranged from -18.3

to +10.0 in patients not previously treated with buffers. Ten patients had a base deficit greater than 5 mEq/litre and three a base excess greater than + 5 mEq/litre. Patients 17 and 18 with base excess values of +13.9 and +8.8 respectively had prior infusion of bicarbonate. The initial results obtained in patients breathing air are summarised in Table 11a.

Correlation with Clinical Observations

Of the 31 patients in whom initial Po_2 measurements were made, restlessness was present in eight. In six of these the Po_2 was 60 mm Hg or less. A Po_2 below 60 was also found in seven of the remaining 23 cases. There was no significant difference in the Po_2 between 12 occasions when restlessness was present and the 25 occasions when it was absent during follow-up ($P > 0.2$).

Cyanosis was present in 11 patients in whom saturations were calculated. On each of these the arterial So_2 was less than 90 per cent and in nine was less than 85 per cent. On the 20 occasions when cyanosis was absent the arterial So_2 was above 85 per cent in all but two. On a further 24 occasions when cyanosis was absent during follow-up the saturation was above 85 per cent on all but two occasions.

The arterial Po_2 in those patients in whom consciousness was impaired was compared with the arterial Po_2 in fully conscious patients both for admission and follow-up data; no significant differences were found. In 11 of the 15 patients who were 'unresponsive' on admission, however, the pH was below 7.30, whereas only two of the remaining cases had a pH below 7.30 ($P < 0.001$). This is illustrated in Figure 2. There was no significant difference in Pco_2 between these two groups.

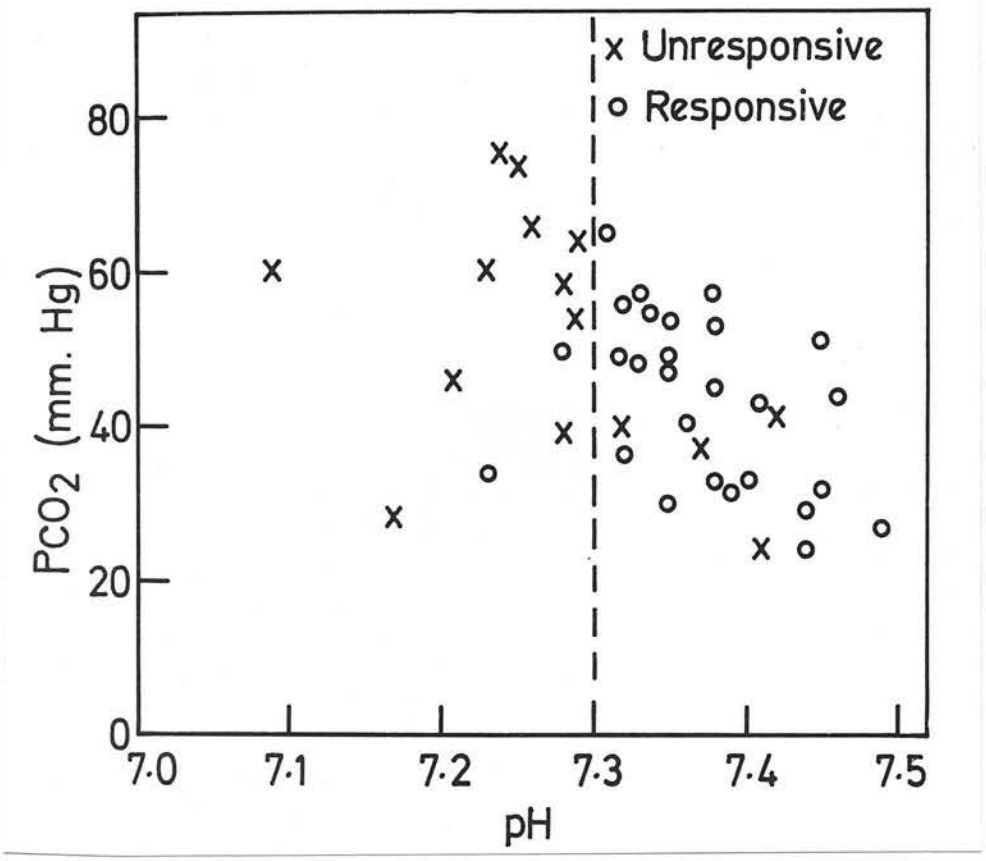

Figure 2

Relation between Pco_2 and pH in 'responsive' o and 'unresponsive' x patients, on admission. pH is significantly different in the two groups ($P < 0.001$).

There was no relationship between the respiratory rate or respiratory score and the blood gas tensions obtained on admission to hospital. There was, however, a significant relationship between pulse rate and Pco_2, both on admission and during follow-up. The combined admission and follow-up data in all patients breathing air or oxygen is shown in Figure 3 ($0.01 > P > 0.001$).

Table 11b shows the blood gas tensions and pH in different radiological groups. In each radiological group mean Po_2 was below and the mean $A\text{-}aDo_2$ greater than normal. Pco_2 varied widely in each. Between groups the differences in the mean of these variables were not significant. A comparison of the blood gas tensions between infants with and without overinflation of the lungs on X-ray likewise did not reveal significant differences.

Effects of Oxygen Therapy

It seems reasonable to assume that oxygen therapy has been effective if an arterial Po_2 within the normal range is obtained, and a Po_2 of 80 mm Hg or more is regarded as meeting this requirement. In Figure 4 arterial Po_2 is plotted against FIo_2 at the time when the arterial sample is taken, and includes all data obtained in the first 48 hours after admission to hospital. Hypoxaemia is usually, but not invariably, relieved by 40 per cent oxygen. In Cases 2, 21, 22 and 45 an inspired oxygen concentration of 40 per cent did not produce an arterial Po_2 over 80 mm Hg.

The effect of relieving hypoxaemia on Pco_2 is shown in Figure 5 in which Po_2 is plotted against the Pco_2 in the same patient during the first 48 hours after admission. As the Po_2 increased after oxygen therapy, there were no significant increases in Pco_2. The values

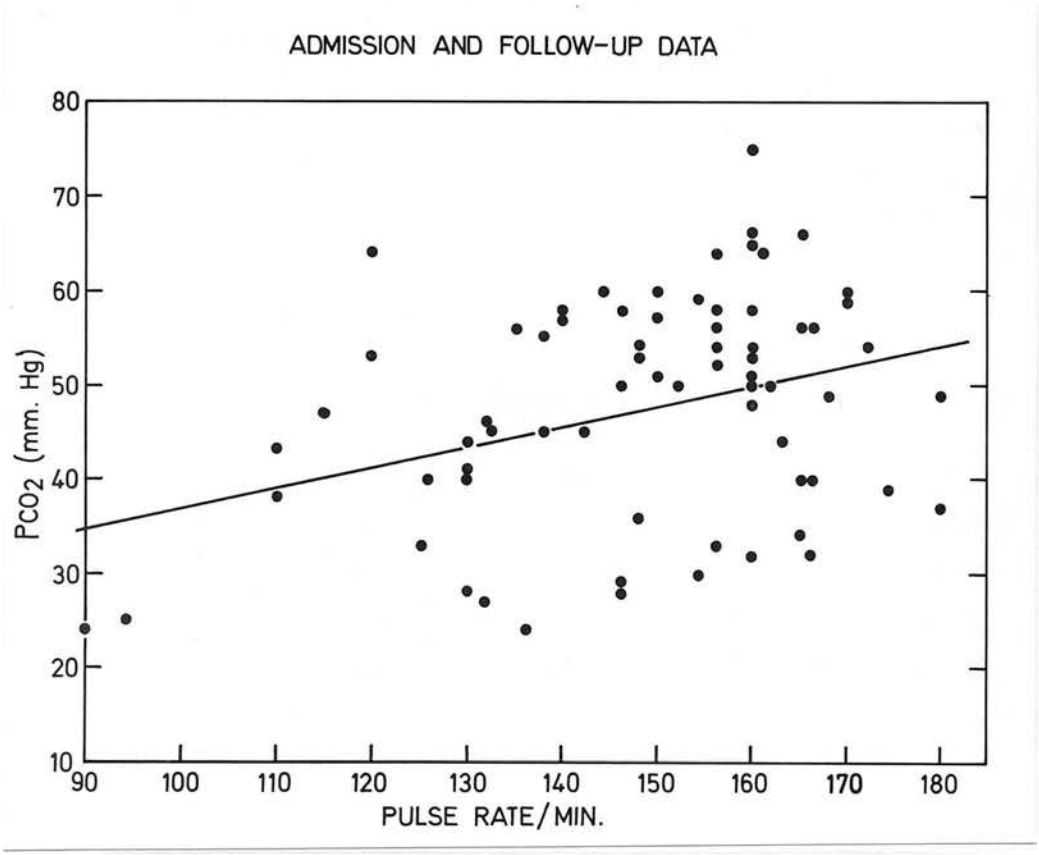

Figure 3

Relation between pulse rate and Pco_2, admission and follow-up data, breathing air or oxygen. (excludes Case 37)

Pco_2 = 0.22 pulse rate + 15.2 r = 0.35, $0.01 > P > 0.001$

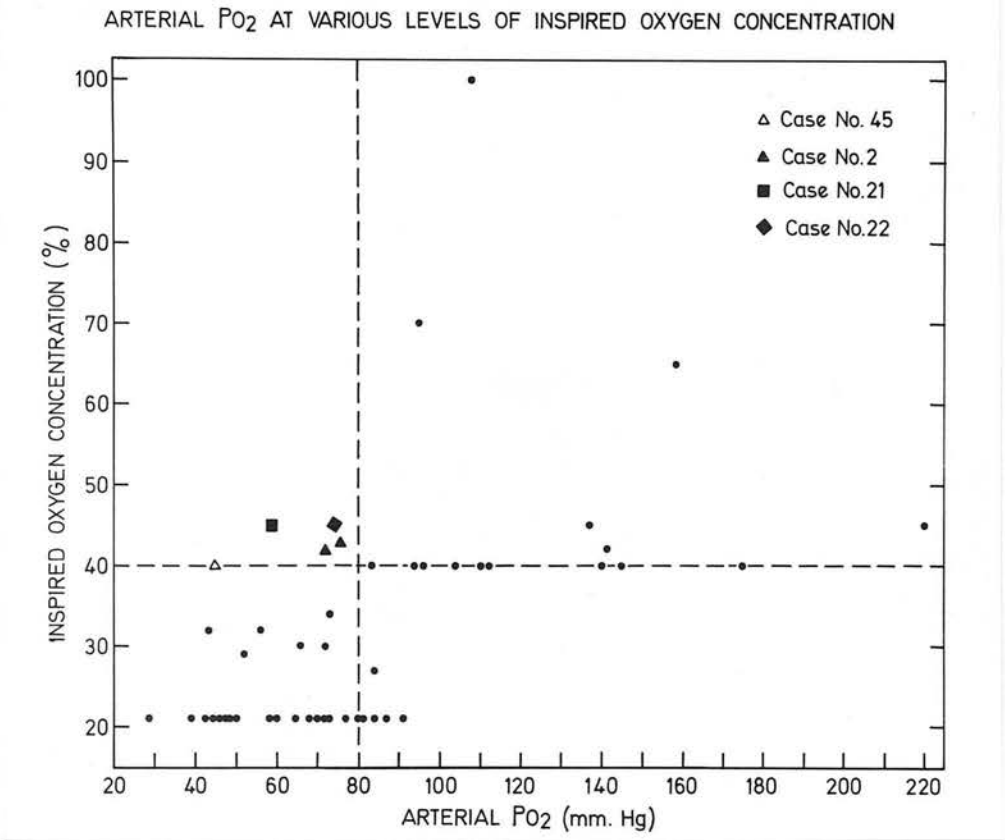

Figure 4

Arterial Po_2 at various levels of inspired oxygen concentration. In Cases 2, 21, 22 and 45 an inspired oxygen concentration of 40 per cent did not produce a Po_2 of more than 80 mm Hg.

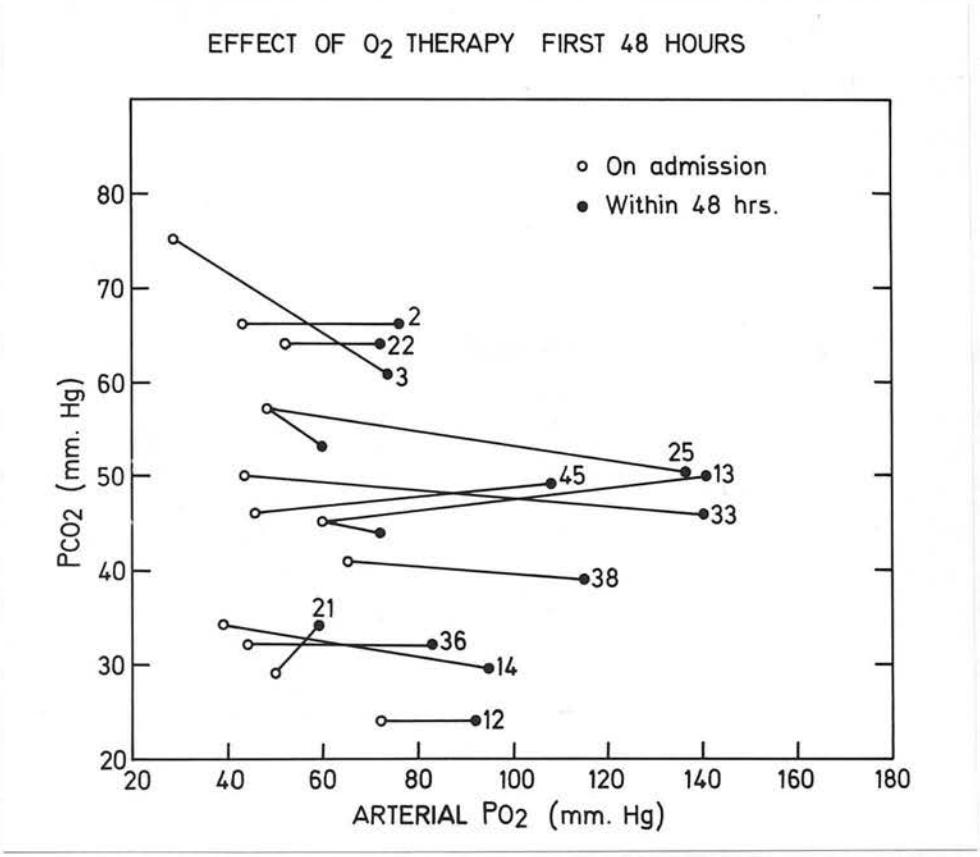

Figure 5

Changes in arterial Po_2 and Pco_2 after oxygen in the first 48 hours.

obtained in patients breathing 40-45 per cent oxygen are given in Table 12. Again the data was obtained within 48 hours of admission to hospital.

ILLUSTRATIVE CASE REPORTS

Case 5

This two-month old infant was admitted to hospital with noisy breathing, refusal of feeds and vomiting of one day's duration. In the preceding three days she had had a 'cold' and nasal discharge. Delivery had been in hospital at term, after a normal pregnancy (birth weight 2.9 Kg). Her early progress had seemed satisfactory.

On examination, she was pale with tachypnoea and grunting respirations. Alae nasae were flaring and there was marked suprasternal and subcostal recession. The chest was overdistended and breath sounds were vesicular with prolonged expiration. Fine crepitations were audible throughout both lung fields. The liver was palpable 4 cm below the right costal margin. No cardiac abnormalities were detected.

A diagnosis of bronchiolitis was made clinically - pneumonic signs were present on a chest X-ray (Plate I). She was nursed in 35-50 per cent oxygen and treated with antibiotics. She remained restless, irritable and distressed and required tube feeding for the first three days. Steroids were prescribed empirically from the day of admission. During feeds, and at any time she was out of her oxygen tent, she became cyanosed. After five days, however, she was well enough to be removed from her oxygen tent, though she was still slightly distressed during feeds. Antibiotics and steroids were stopped after one week and she was discharged home fourteen days following admission.

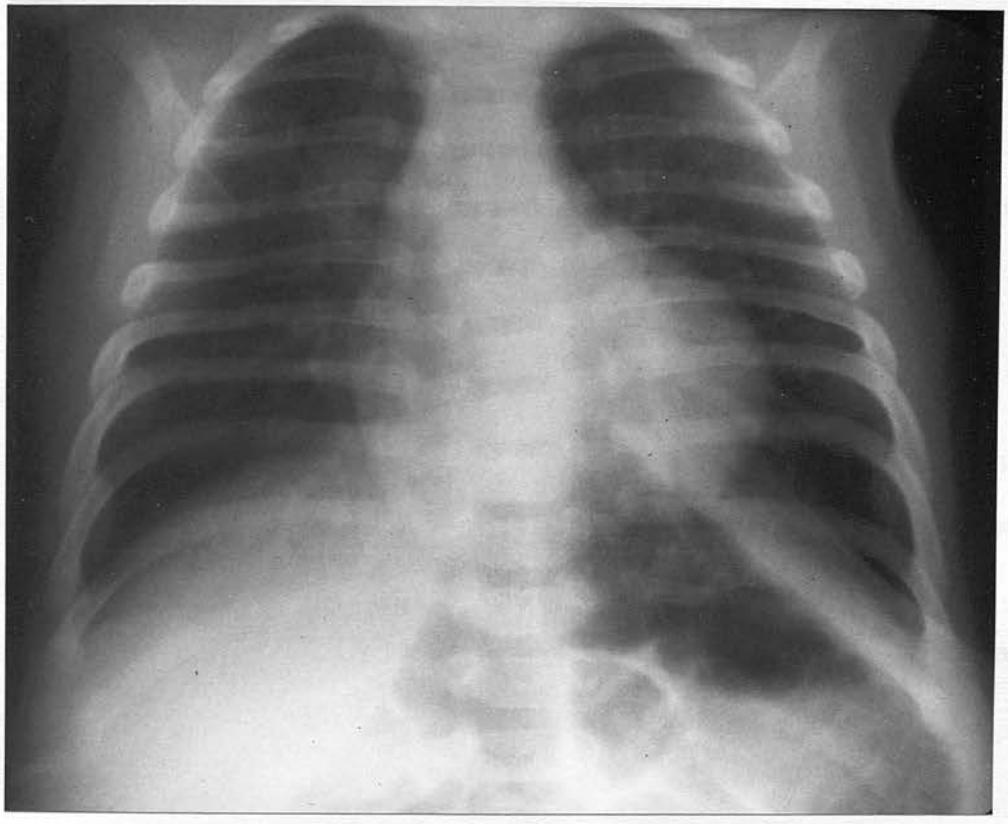

Plate I

Chest X-ray on admission to hospital (Case 5). Appearances were normal three weeks later.

Figure 6 shows that ventilatory failure with a peak Pco_2 of 65 mm Hg was present for the first three days. Acid-base status had returned to normal by day four, but the respiratory rate remained over 70 per minute until day six when it suddenly dropped to 40 per minute. Chest signs gradually disappeared. She became more active and was feeding normally at the time of her discharge on the fourteenth day after admission.

Case 13

This four-month old infant was admitted to hospital with a two day history of cough, wheeze and nasal discharge. He was born in hospital at term after a normal pregnancy and delivery (birth weight 3.1 Kg).

On examination, he was febrile (temperature 38^{o}C) but was pink in air with a constant distressing cough. Alae nasae were in use, accompanied by suprasternal and subcostal indrawing. The chest was overinflated, percussion note was resonant and fine crepitations were audible throughout both lung fields. No other abnormalities were detected. Chest X-ray showed consolidation of the posterior segment of the right upper lobe (Plate II) with over-inflation of the lung bases.

He was treated in 40 per cent oxygen and antibiotics prescribed. Respiratory distress persisted for two days, but thereafter he recovered gradually and chest signs had disappeared by day six. He was active and feeding normally at the time of his discharge ten days after admission to hospital.

The time course of acid-base changes during the course of his illness is shown on Figure 7. The trends outlined were seen in several of the less severely affected infants.

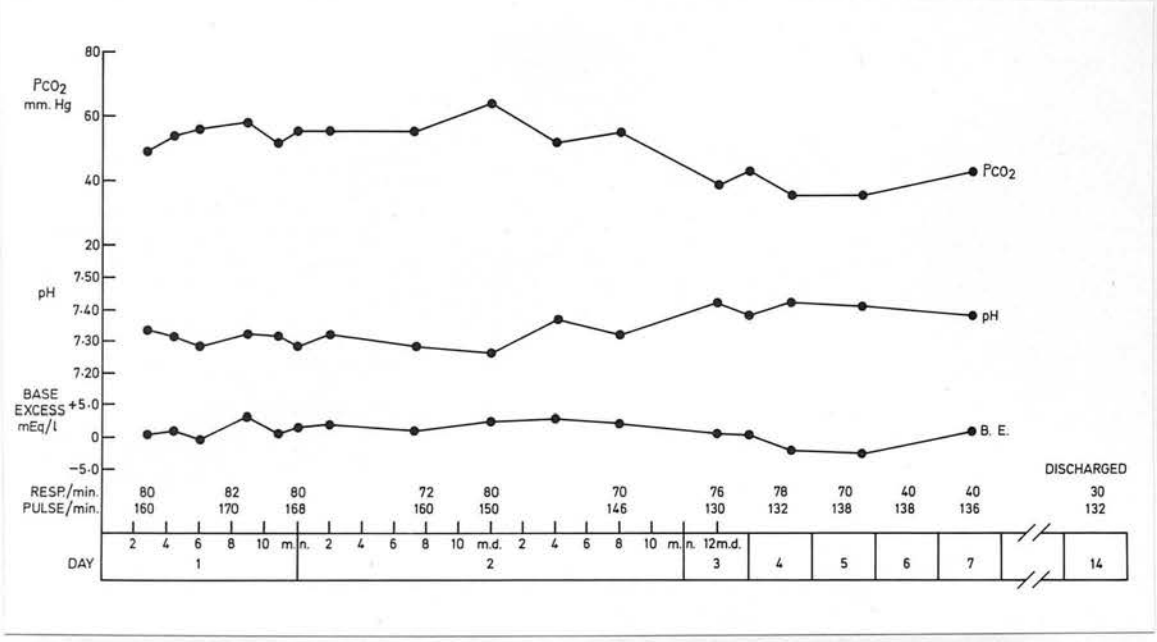

Figure 6

Changes in acid-base variables during course of severe bronchiolitis (Case 5) measured in approximately 40 per cent oxygen.

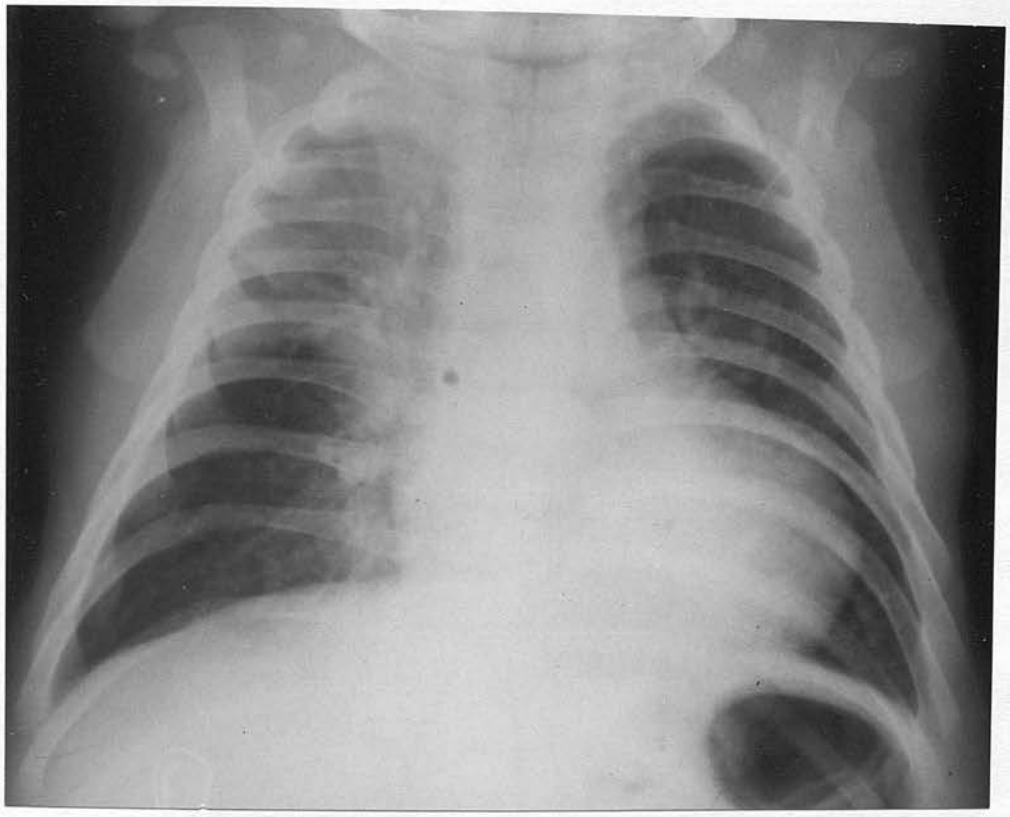

Plate II

Portable chest X-ray soon after admission to hospital (Case 13).

Appearances were normal two weeks later.

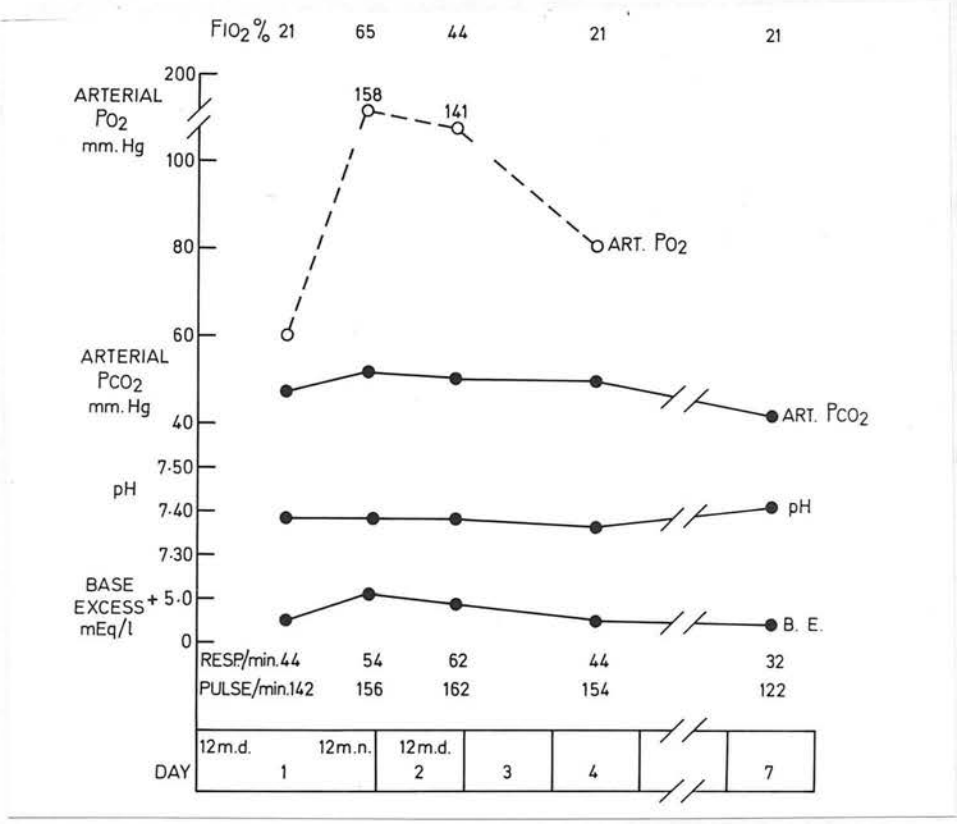

Figure 7

Changes in acid-base variables during course of moderately severe bronchiolitis (Case 13).

DISCUSSION

The clinical aspects of bronchiolitis in infants have been described previously (Hubble and Osborn, 1941; Garrow and Fawcett, 1953; Morrison, 1957; Elderkin et al., 1965; Wright and Beem, 1965; Lancet Leading Article, 1969). The infants described here were all moderately or severely ill with acute lower respiratory tract infection. It is unfortunately not possible to categorise them further on an aetiological basis as the information available is incomplete. In view of the ages of the patients affected, the seasonal incidence, and the frequent history of family contacts with coryzal symptoms, however, it seems likely that viruses were often of primary importance. Since the isolation of the respiratory syncitial virus (RSV) from infants with bronchiolitis (Chanock et al., 1961) its importance both in bronchiolitis (McClelland et al., 1961; Holzel et al., 1963; Elderkin et al., 1965) and pneumonia (Loda et al., 1968) in infancy has become increasingly recognised. The radiological features encountered in infants with proven respiratory syncitial virus infection (Rice and Loda, 1966) are also similar to those seen here. Any possible role of RSV or other viruses in these cases is, however, purely conjectural. Similarly, the importance of bacterial pathogens is uncertain. There has been a tendency in some reports to emphasise the viral nature of respiratory illnesses in children and to minimise the role of bacteria. The relevance of organisms isolated from nasal and throat swabs is always questionable, while failure to identify certain bacterial pathogens does not necessarily mean that they are not implicated; in the present series many patients had been treated with antibiotics before being referred to hospital, and certain organisms, notably Haemophilus influenza, were not looked for specifically.

The variation in clinical severity in these patients makes it difficult to compare this with other published series. In general, patients were more severely ill than those of Reynolds (1963) but perhaps less ill than some described by Jones et al. (1968). Downes et al. (1968) subdivide their cases on the basis of clinical and blood gas findings into those in whom ventilation is adequate and others requiring mechanical assistance to ventilation. Had the criteria of these authors been applied to this series, mechanical ventilation would have been used on many more occasions. The policy here was deliberately much more conservative, however, as a 24-hour nursing and blood gas service was not available.

The results present an opportunity to assess the value of clinical signs in estimating the levels of arterial Po_2, Pco_2 and pH in these children. In addition, the possible mechanisms of hypoxia and acidosis can be discussed and the importance of oxygen therapy assessed. Some indication of the value of blood gas measurements in guiding treatment and indicating prognosis are also possible.

Correlation with Clinical Features

Morrison (1955) suggested that restlessness is a valuable sign of hypoxia in such cases, but on the basis of direct measurements in arterial blood this suggestion cannot be fully supported. Although six of seven children who were restless had a Po_2 of 60 mm Hg or less, seven of the remaining patients also had a Po_2 less than 60 mm Hg. Four of this latter group showed impairment of consciousness level and were "unresponsive", whereas none of the restless infants showed this sign. Case 14, aged two weeks, was severely hypoxaemic without being restless. In this age group Davis (1966) has drawn attention to the fact that

restlessness is not a reliable sign of hypoxaemia. Morrison (1955) determined the oxygen saturation of "arterialised" capillary blood on 31 occasions in 18 children and found that restlessness was present much more often when the saturation was below 80 per cent. It is possible that despite the measures she used to ensure local vasodilation, the capillary blood was not an adequate substitute for arterial blood, at least in regard to So_2.

The reliability of cyanosis as a clinical sign is somewhat surprising. It is not an unequivocal sign of hypoxia and is only a sign of hypoxaemia in certain situations. The blue discolouration of the skin and mucous membranes is caused by the absolute concentration of reduced haemoglobin in the tissues - with threshold levels of 3-5 g per 100 ml. It is thus likely to be a late sign of hypoxaemia, and may never appear in anaemic patients. Conversely, cyanosis may be present in patients with polycythaemia or low cardiac outputs however high the arterial oxygen tension. The spectral qualities of artificial lighting (Kelman and Nunn, 1966) and the presence of foetal haemoglobin further complicate the value of cyanosis as a clinical sign of hypoxaemia in these infants. Despite these reservations, cyanosis was the most reliable sign of severe hypoxaemia. When it is present the arterial So_2 is always below 90 per cent and most often below 85 per cent. These conclusions still hold if the So_2 is corrected on the assumption that 50 per cent of haemoglobin was of foetal type in any patient under four months of age.

Most of the "unresponsive" patients were breathing oxygen-enriched air at the time of assessment, with partial or complete correction of hypoxaemia. It is not possible, therefore, to relate this sign to the degree of hypoxaemia which may have existed before starting oxygen therapy. The metabolic acidosis present in these patients may well

have resulted from hypoxia (see Section VI). Hypothermia and hyponatraemia were additional problems in these patients, and those presenting with circulatory collapse are similar to the cases described by Jones et al. (1968), though none showed a comparable degree of renal failure.

Of the other clinical signs evaluated, respiratory rate bore no relationship to either Po_2 or Pco_2. The significant relationship between the pulse rate and Pco_2 confirms Reynolds' (1963) findings for bronchiolitis. At pulse rates greater than 160 per minute many of these infants have significant ventilatory failure. The allocation of the numerical score to clinical signs was used by Apgar (1953) to evaluate the clinical severity of asphyxia in the newly born. Here a modification of the methods of Silverman and Anderson (1965) and Dabbous et al. (1966) was used to evaluate some clinical signs of respiratory distress. The lack of correlation between the respiratory signs score and Po_2 and Pco_2 is not surprising since the conventional signs of respiratory distress used in constructing the clinical score are more likely to have been caused by an increased minute volume of ventilation, often with some obstruction to the airways. Many such infants show an increase in minute volume of ventilation despite an increase in airways resistance and in dynamic compliance (Krieger and Whitten, 1964; Phelan et al., 1968; Wohl et al., 1969) and an overall increase in the work of breathing (Krieger, 1964).

The Effects of Oxygen Therapy

Reynolds (1963b) suggested than an inspired oxygen concentration of 40 per cent can raise the arterial Po_2 above 100 mm Hg in babies with bronchiolitis. In four cases (2, 21, 22 and 45) an inspired oxygen concentration of 40-45 per cent did not produce an arterial Po_2 over

80 mm Hg. None had congenital cardiac defects with right-to-left intracardiac shunting of blood, but Cases 21 and 45 showed extensive pneumonic changes on chest X-rays, which presumably resulted in shunting of blood through poorly ventilated areas of lung. Chest radiographs of Cases 2, 21 and 22 are illustrated in Plates III, IV and V. In patients 2 and 22 severe shock may have been a contributory factor. In Reynolds' (1963b) ten cases, chest X-rays were either normal or showed hyper-inflation. Only two showed areas of collapse. The administration of 40 per cent oxygen in these resulted in a Po_2 greater than 100 mm Hg in nine cases. Our findings are therefore not at variance. Forty per cent oxygen is usually, but not invariably, effective in relieving hypoxaemia in acute lower respiratory tract infection in infants. Although inspired oxygen concentrations of 40 per cent can be produced in incubators at 3-4 litres per minute oxygen flow, similar levels in tents are often not achieved in routine practice (Simpson and Russell, 1967). It has been suggested that an arterial Po_2 of 50 mm Hg will prevent death in an acute exacerbation of infection in an adult with chronic bronchitis (Hutchison, Flenley and Donald, 1964). These children with acute lower respiratory tract infections differ, however, in many ways from adults with chronic bronchitis; they are not acclimatised to chronic hypoxaemia and the tolerance to severe hypoxia seen in the immediate neonatal period (Mott, 1961) has not been shown to persist. These children with lower Pco_2 levels will be at greater risk from hypoxia in theory at least, for a low Pco_2 is a potent constrictor of the cerebral circulation. It seems, therefore, that an inspired oxygen concentration greater than 40 per cent may occasionally be necessary to provide a safe Po_2. The danger of pulmonary epithelial damage (the Lorraine Smith / 1899 / effect) from uncontrolled high concentrations

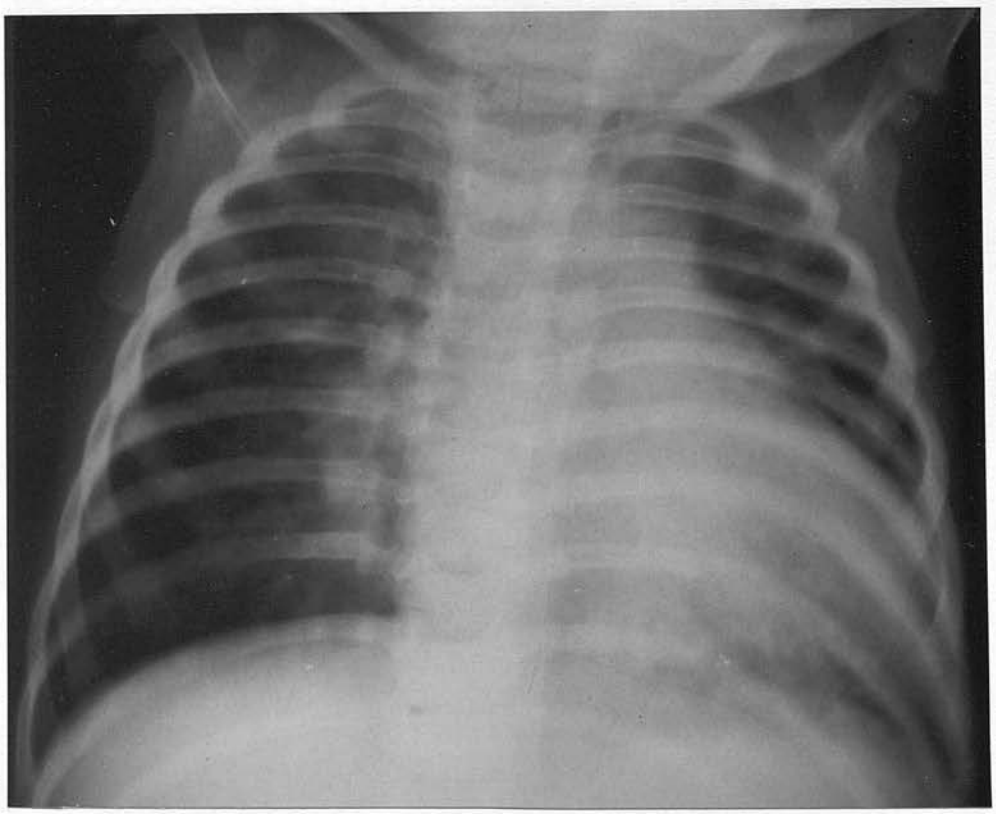

Plate III

Chest X-ray on admission to hospital (Case 2). 40 per cent oxygen did not relieve hypoxaemia.

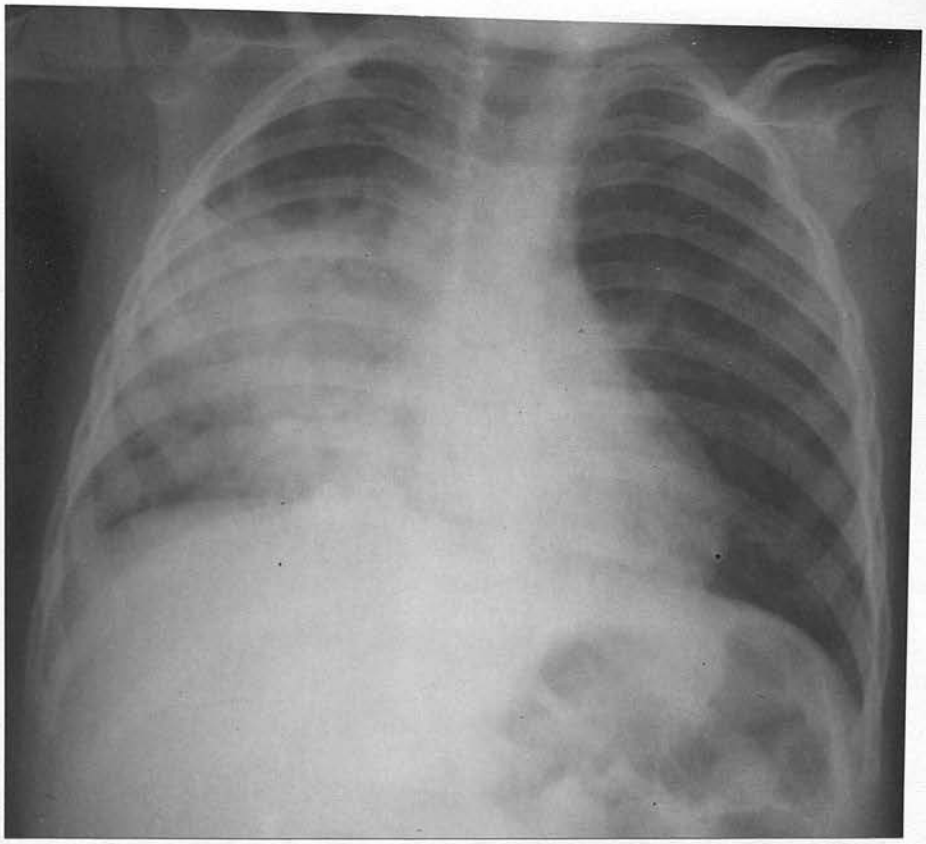

Plate IV

Chest X-ray on admission to hospital (Case 21). 40 per cent oxygen did not relieve hypoxaemia.

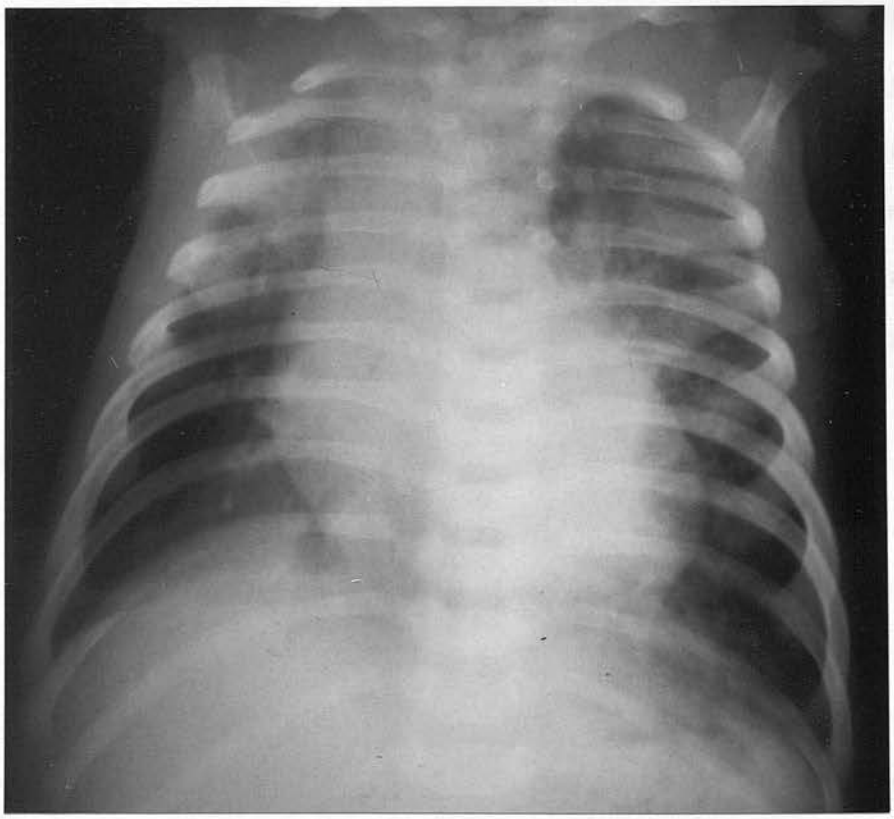

Plate V

Chest X-ray on admission to hospital (Case 22). 40 per cent oxygen did not relieve hypoxaemia.

of oxygen has become increasingly recognised in recent years (New England Journal of Medicine, Leading Article, 1967) but there is no evidence that this effect is of importance at oxygen concentrations below 60 per cent.

Co_2 Narcosis

An increase in Pco_2 during oxygen therapy is a well recognised danger in treating respiratory failure in the adult (Donald, 1949; Comroe et al., 1950; Westlake et al., 1955). Reynolds (1963b) described ten cases of bronchiolitis in infants and noted a high Pco_2 (over 45 mm Hg in seven, but in none of his cases did the Pco_2 rise significantly after oxygen therapy. In 24 cases the Pco_2 was above 45 mm Hg on admission, and here also oxygen therapy did not produce a further rise in Pco_2 (Figure 5; Table 12). This confirms Reynolds' experience and again suggests that in acute lower respiratory infections in infancy there is no danger of death from Co_2 narcosis as a result of oxygen therapy, despite the high Pco_2 found in many cases.

Mechanisms of Hypoxaemia

A low arterial Po_2 in these cases could result from alveolar hypoventilation as shown by a raised arterial Pco_2. Alternatively, hypoxaemia could result from an imbalance of ventilation and perfusion in the lungs, with limitation of available area of blood gas interface. The first mechanism of hypoxaemia can be examined by noting the relationship between Po_2 and Pco_2 on admission. From Figure 8 it is seen that, as expected, the readings are negatively correlated at a low level of significance ($0.01 > P > 0.001$). It therefore seems that hypoventilation alone is a rather inadequate explanation for the hypoxaemia found in these cases.

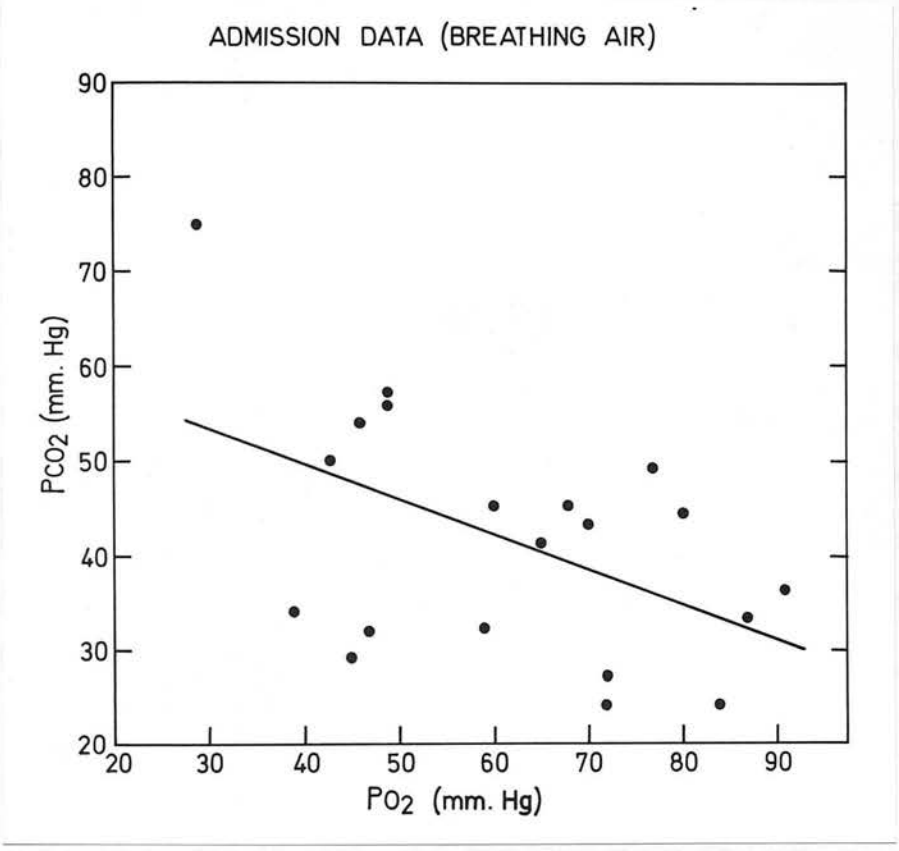

Figure 8

Relation between arterial Po_2 and Pco_2 on admission, breathing air.

$$Pco_2 \text{ mm Hg} = -0.37\ Po_2 \text{ mm Hg} + 64.4$$

$$r = -0.50;\ 0.05 > P > 0.02$$

In Figure 9 the A-aDo_2, calculated on the assumption of a respiratory quotient of 0.8, is plotted against the arterial Po_2 when breathing air. The relation is significant ($0.01 > P > 0.001$) suggesting that hypoxaemia is also caused by ventilation/perfusion imbalance with limitation of blood gas interface.

Prognostic Value of Low Po_2

The Po_2 was only known in three of the five deaths - Case 36, Po_2 47 breathing air, Case 44, Po_2 112 breathing 40 per cent oxygen, and Case 45, Po_2 45 breathing 40 per cent oxygen. In seven others the Po_2 was under 50 mm Hg, yet all survived. However, before assuming that a low Po_2 is not of grave prognostic importance it must be recalled that all these patients were treated with oxygen, and in some cases this was being given when the initial readings of Po_2 were made. The severity or duration of hypoxia before therapy was started is unknown.

Hypercapnia and Acid-Base Balance

In 19 of the 45 cases the Pco_2 was above 50 mm Hg on admission to hospital (Table 11) which confirms Reynolds' (1963) observations that severe respiratory failure is not uncommon in these cases. The consequences with regard to oxygen therapy have already been discussed. Eleven of the 45 children were hyperventilating, the Pco_2 being below 35 mm Hg on admission. This is reminiscent of the hyperventilation seen in acute lobar pneumonia in the adult (Meakins and Davis, 1925).

The variation in Pco_2 at various levels of Po_2 in the different cases is shown in Figure 8. In Cases 21, 26 and 36 severe hypoxaemia persisted in the presence of considerable hyperventilation. Conversely,

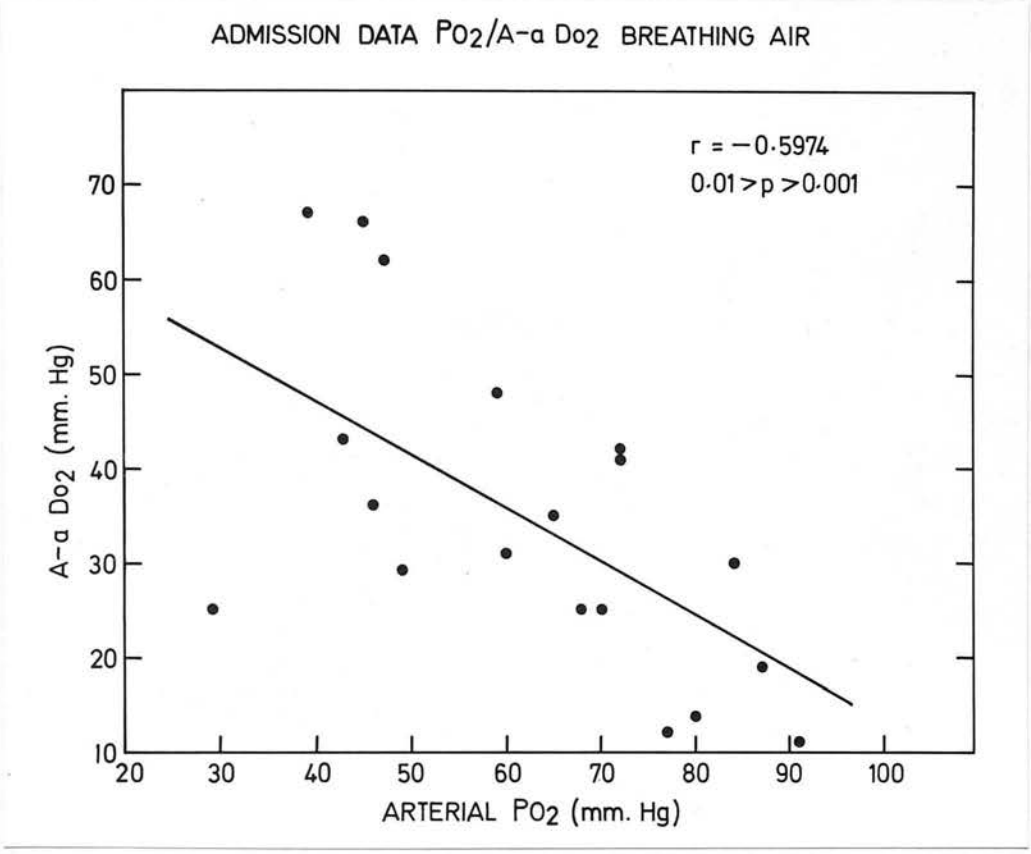

Figure 9

Relation between A-aDo_2 and arterial Po_2 when breathing air, on admission.

$$A\text{-}aDo_2 \text{ mm Hg} = -0.56\ Po_2 \text{ mm Hg} + 69.2$$

$$r = -0.60\ ;\ 0.01 > P > 0.001$$

in Cases 10, 12, 23 and 29 similar levels of Pco_2 were associated with normal values for Po_2. Thus, in these cases hyperventilation succeeded in preventing hypoxaemia.

In six of the 45 cases the pH was below 7.25 on admission. The significant relationship between the Pco_2 and base excess (Siggaard-Andersen, 1963) on admission to hospital is shown on Figure 10. Negative base excess values were usually associated with low Pco_2 with the exception of Case 30, Pco_2 59 mm Hg, base excess -12.6 mEq/litre, an infant with hypernatraemia and circulatory collapse. Hyperventilation could be due in part at least to an acidotic drive to respiration. It is also possible that the inflammatory process in the lungs was a direct cause of both the hyperventilation and the metabolic acidosis. It seems more certain that hypoventilation (as shown by the high Pco_2 levels in Figure 10) is a primary result of the pulmonary lesions. The positive values of base excess, metabolic alkalosis suggest that renal reabsorption of bicarbonate is an important defence mechanism against acidosis in children, as it is in the adult (Barker et al., 1957; Refsum, 1964). Only one infant, Case 18 with a Pco_2 of 51 mm Hg and base excess of +10.0, had vomited excessively following admission to hospital.

The rate of development of this increase in base excess in eight cases with initially high Pco_2 levels is seen in Table 13. The first values of Pco_2 and base excess are those obtained on admission and varied in time from the 2nd to the 8th day of the illness. In five of these cases the base excess was in the normal range (-3.3 to +2.2 mEq/litre) (Siggaard-Andersen, 1964). In these children, therefore, none of whom had been given bicarbonate therapy, the base excess which is directly related to the plasma bicarbonate can rise after eight days of illness. These figures emphasise that a corresponding rise in base excess is an important defence against respiratory acidosis in these children

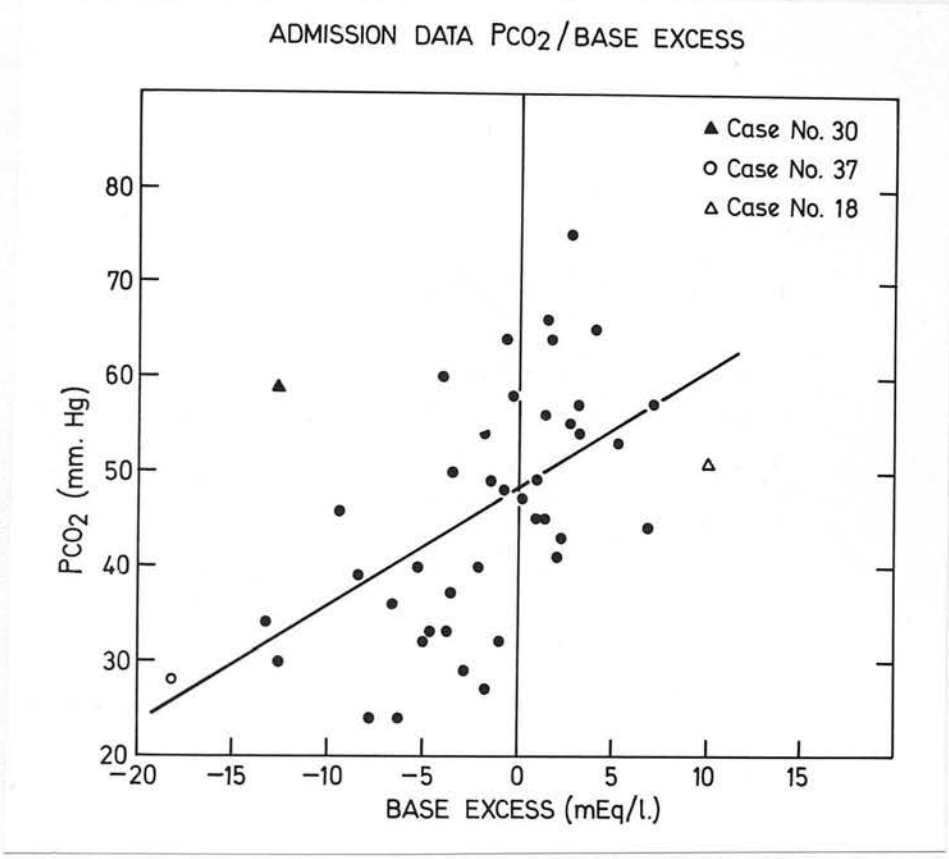

Figure 10

Relation between arterial or arterialised capillary Pco_2 and base excess on admission, excluding cases treated with sodium bicarbonate.

Pco_2 mm Hg = 1.15 Base Excess mEq/l + 48.1

$r = 0.53$; $0.01 > P > 0.001$

The Mechanism and Prognostic Value of Acidosis

The causes of a metabolic acidosis in these children may well be complex. The results in Table 11, however, allow an examination of the proposal that anaerobic metabolism, with production of lactic acid, produced a metabolic acidosis in these children (Huckabee, 1958). In cases 14 and 45, a low Po_2 is associated with striking metabolic acidosis (respective base excess values -13.4, -9.5). Case 14 had had severe diarrhoea from soon after birth. Two of the remaining cases with severe metabolic acidosis (Cases 19 and 37) and a normal Po_2 were breathing oxygen. In three cases (12, 23 and 24) however, values for base excess lay between -5 and -10 mEq/litre, yet the Po_2 was between 70 and 100 mm Hg. Aspirin administration was not a feature in these cases, but there was vomiting and diarrhoea in Cases 12 and 24. Arterial blood lactate and pyruvate measurements were made in two of the 45 patients (Cases 37 and 45) (Section VI). There is, therefore, insufficient information to say whether or not hypoxia was a potent cause of metabolic acidosis in all of these children.

Simpson and Flenley (1967) emphasised the grave prognostic significance of a pH below 7.20 and a Pco_2 above 65 mm Hg in their series, which included three cases of staphylococcal pneumonia. In the five deaths during the present study, low pH values on admission were found in Case 30 (pH 7.09) and Case 45 (pH 7.21). In Cases 36, 42 and 44 initial pH values were above 7.35, but fell during the course of their illnesses to below 7.20. The precise cause of death in these infants is uncertain. Tricuspid incompetence (Case 36), agammaglobulinaemia (Case 42), and 'shock', anaemia, hypernatraemia, hypothermia intestinal infection and retention of secretions in the remaining infants (Cases 30, 44 and 45) may all have contributed to a fatal outcome.

SUMMARY

Arterial blood gas tensions and pH changes were studied in 45 children under three years with acute lower respiratory tract infections. The results confirm most of the findings of Simpson and Flenley (1967). Clinical signs of respiratory distress were found to be of limited value as an indication of the blood gas level in individual cases. Cyanosis, which was invariably present when the oxygen saturation was below 85 per cent, was the most reliable sign of severe hypoxaemia.

The administration of 40-45 per cent oxygen failed to produce normal levels of arterial oxygen tension in four cases. It cannot, therefore, be assumed that 40 per cent oxygen will always be sufficient for treating acute lower respiratory tract infections in infancy and childhood. The results confirm that there is no danger of producing carbon dioxide narcosis during oxygen therapy in these cases, although some carbon dioxide retention is commonly present.

Imbalance of ventilation and perfusion in the lungs and hypoventilation were important causes of hypoxaemia. A compensatory rise in base excess was a defence against respiratory acidosis in these children. The results also confirm the grave prognostic importance of a low pH. In three patients without congenital abnormalities, 'shock', anaemia, hypernatraemia, hypothermia and retention of secretions in the airways may have contributed to a fatal outcome.

S E C T I O N II

Chapter 2

STAPHYLOCOCCAL PNEUMONIA

STAPHYLOCOCCAL PNEUMONIA

INTRODUCTION

Primary staphylococcal pneumonia is a severe bacterial infection characterised by toxicity and a tendency to formation of abscesses, empyema, pneumothorax and cysts. It was first described as an entity by Chickering and Park during the 1919 pandemic of influenza. These authors stressed the virulence of the organism in these infections and the high mortality rate which ensued, 50 per cent, in their series of 153 adults. This compared with a mortality of only 10-15 per cent for all other types of pneumonia.

In recent years several series of cases of staphylococcal pneumonia in infancy and childhood have been reported. (Disney et al., 1956; Forbes and Emerson, 1957; Pryles, 1958; Hendren and Haggarty, 1958; Koch et al., 1959; Groff et al., 1966). In each the importance of early diagnosis and vigilant clinical observation to detect complications during the course of the disease is emphasised. Stevens et al. (1965) described the occurrence of severe ventilatory failure in babies with staphylococcal pneumonia, and the need for measurement of blood gas tensions to guide clinical decisions on management - a view reaffirmed by Jones et al. (1968). Here, serial measurements of blood gas tensions and pH are presented together with the clinical manifestations in five infants with staphylococcal lung disease.

Patients

The five patients (three females and two males) were between three and 24 weeks old. They were admitted to the Royal Hospital for Sick Children, Edinburgh, during the winter months from 1966 to 1968. Their

main symptoms prior to admission to hospital are shown on Table 14. Initial clinical observations are summarised in Table 15. A provisional diagnosis of staphylococcal pneumonia was made in each case on the basis of the clinical and X-ray findings, and treatment started before the results of bacteriological investigations were known. In Cases 1-4 the diagnosis was confirmed bacteriologically. Case 5 is retained in the series, however, despite the lack of bacteriological confirmation because of the characteristic clinical course of her illness. The results of bacteriological and other laboratory investigations are shown in Table 16.

None of these infants was considered well enough to be studied in air. Initial arterial blood samples were taken at the time of admission to hospital (Cases 1-3), on day 2 (Case 5), and day 6 (Case 4) each patient having breathed oxygen for at least fifteen minutes. Subsequent samples were taken as determined by clinical progress.

RESULTS

Of the five infants in the series, only one (Case 5) survived. Cases 1, 2 and 4 died during the acute phase of their illnesses, and Case 3 died after several weeks in hospital at a time when recovery seemed more likely.

Initial Blood Gas Tensions and pH

Initial measurements and calculated data are shown in Table 17. Despite an inspired oxygen concentration of 40 per cent or above the Po_2 remained below 80 mm Hg in two patients (Cases 2 and 4). Pco_2 ranged from 74 to 90 in Cases 1-4, and was normal in Case 5. pH values

lay between 7.14 and 7.29. Respiratory acidosis, partially compensated in Cases 1 and 3, was the main acid-base disturbance in Cases 1 and 4, whereas a pure metabolic acidosis, base deficit 10.4 mEq/litre, was present in Case 5.

Subsequent Blood Gas Tensions and pH

The clinical courses of Cases 2 and 5,described in Tables 18 and 19, illustrate some of the main findings on follow-up. The blood gas values show the extreme degree of the ventilatory failure which developed in Case 2, and the difficulty of maintaining adequate oxygenation with the administration of increased oxygen to the inspired air. The positive values of base excess represent partial metabolic compensation for respiratory acidosis.

Table 19 shows that adequate ventilation was maintained initially in Case 5, and that severe metabolic acidosis was the main acid-base abnormality. As cyanosis was present in room air initial Po_2 measurements were made in 40 per cent oxygen. Despite clinical and radiological improvement hypoxaemia breathing air persisted for several weeks after admission to hospital. The chest X-ray appearances in these two patients are shown in Plates VI and VII.

A detailed account of the clinical courses of the five infants is presented:

Case 1 This six-week-old infant was moribund and collapsed on admission. He was given 100 per cent oxygen by face mask followed by intermittent positive pressure ventilation with a Bird ventilator. Chloramphenicol and cloxacillin were given in full dosage intramuscularly from the

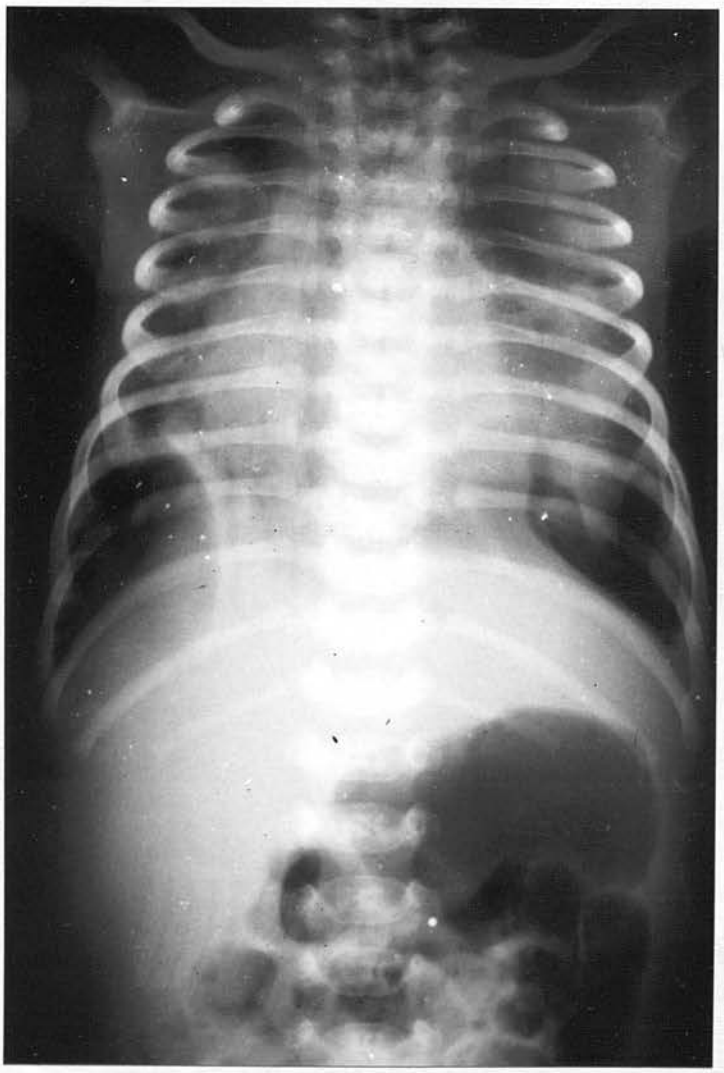

Plate VI

Staphylococcal Pneumonia: Chest X-ray appearance in Case 2, during IPPB.

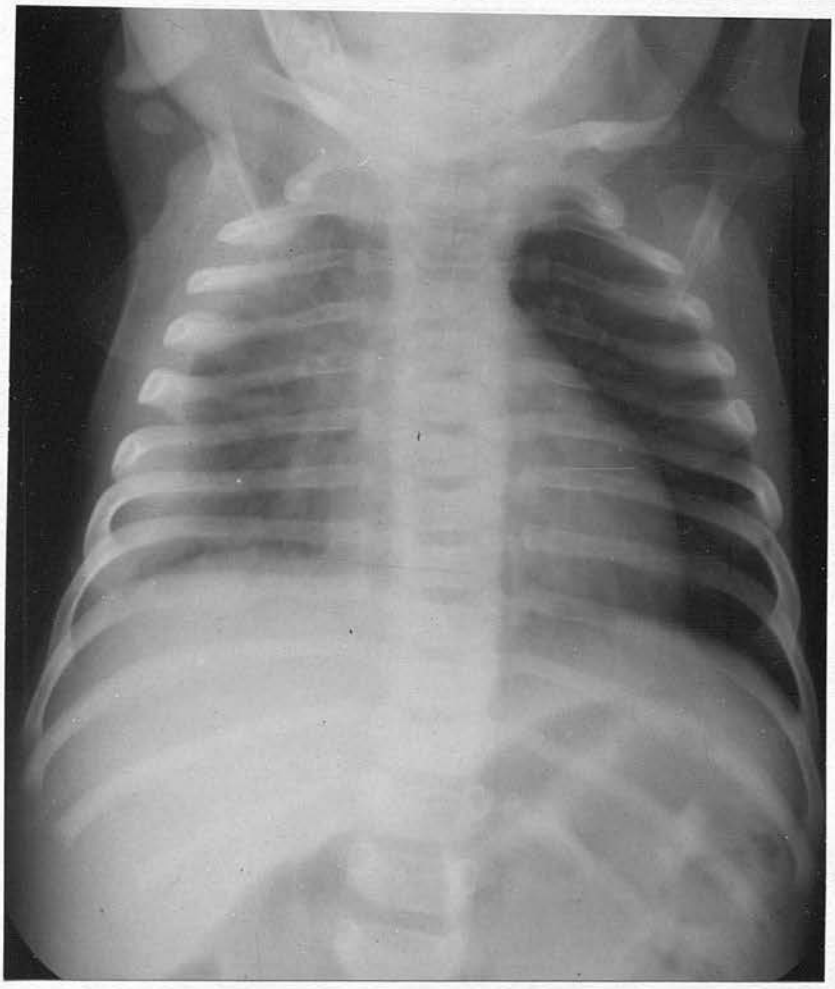

Plate VII

Staphylococcal Pneumonia: Serial Chest X-ray changes (Case 5).

A: On admission

outset in addition to hydrocortisone 50 mg six-hourly. He was rewarmed gradually over the following twelve hours, and 5 per cent dextrose was given concurrently to correct dehydration and maintain the blood glucose within normal limits. IPPB was continued for one day, by which time his Pco_2 had fallen to 52 mm Hg and pH risen to 7.38. Thereafter, he was nursed in 50-60 per cent oxygen with high humidity. There was apparent clinical improvement over the next four days, though radiologically pneumonic changes had increased in both lungs. There was gradual deterioration thereafter with recurrent episodes of apnoea and cyanosis. IPPB was restarted on the sixth day. It was not possible to achieve adequate ventilation and he died eight days after admission to hospital. At necropsy there was extensive consolidation throughout both lungs and a large right-sided empyema. Pseudomonas, E. coli and penicillin-sensitive staphylococci were isolated from the empyema fluid.

Case 2 (see also Table 18) This three-week-old baby was cyanosed, limp and unresponsive on admission to hospital. His respirations were rapid and grunting, his cry weak and his head moderately retracted. There was costal and neck recession, and coarse crepitations were audible throughout both lung fields. Chest X-ray showed extensive bilateral bronchopneumonia with a small left pneumothorax. Oxygen was given by face mask initially and gradually his colour improved. He was then nursed in an Oxygenaire incubator with an ambient oxygen concentration of 50-70 per cent. Cloxacillin, ampicillin and later steroids were given in full dosage. In the first 24 hours his Po_2 remained near 50 mm Hg, and his Pco_2 between 70 and 80 mm Hg. He became more active and less distressed during this period. At twenty-seven hours his Po_2 was 58 mm Hg and his

Pco_2 had fallen to 56 mm Hg. Improvement was not maintained. His condition deteriorated between thirty-four and thirty-six hours, Po_2 falling to 45 mm Hg and Pco_2 rising to 100 mm Hg. Tracheo-bronchial aspiration was then performed and thick mucopus obtained. Intermittent positive pressure respiration using the Bird respirator was started, but death occurred several hours later.

At autopsy the trachea was normal but both main bronchi contained thick mucopus. Both lungs were partially collapsed and showed extensive patchy consolidation. A large empyema, from which staph. pyogenes was cultured, occupied the left pleural cavity. There was marked dilatation of the right atrium and moderate dilatation of the right ventricle. The heart and great vessels were otherwise normal. No other abnormalities were detected.

Case 3 This five-week-old infant was critically ill with a marked degree of toxicity and respiratory embarrassment on admission to hospital. She was intubated at the outset, and mucopurulent secretions aspirated from the tracheo-bronchial tree. She was then nursed in 50-60 per cent oxygen with high humidity and treated with chloramphenicol, cloxacillin and ampicillin. Control of secretions presented a considerable problem during the first week and she was re-intubated on several occasions. There was gradual clinical and radiological improvement, but from time to time severe bouts of coughing followed by collapse required prompt treatment. She collapsed and died during one of these some nine weeks after admission to hospital.

At autopsy the trachea and bronchi were full of mucopurulent material. Widespread pneumonic changes were present throughout both lungs with bullae formation in the right lower lobe. No organisms were isolated on culture.

Case 4 This infant was readmitted to hospital nine days after discharge, following apparent recovery from proven staphylococcal pneumonia. She was treated with ampicillin and cloxacillin from the outset, and nursed in an oxygen tent with high humidity. Her condition caused no real concern until the sixth day when she suddenly became more distressed and toxic. At that stage blood gas analysis indicated a severe degree of ventilatory failure. She collapsed and died while preparations were being made for assisted ventilation.

At post mortem a little mucoid material was present in the trachea but there was no pus in the bronchial tree. Both lungs were over-distended and there were patchy areas of collapse. No other abnormalities were detected.

Case 5 (see also Table 19) This six-month-old infant was extremely pale, with some peripheral cyanosis, on admission to hospital. Her respirations were rapid and shallow, approximately 80/minute, and her pulse rate was 210/minute. Rectal temperature was 42°C. Her throat was reddened and there was considerable intercostal indrawing. Air entry was diminished on the right, and fine crepitations were audible throughout the right lung field. No abnormalities of precordial pulsation or cardiac murmurs were detected. The liver was not enlarged and there was no peripheral oedema. Chest X-ray showed a right-sided pleural effusion and associated consolidation. She was nursed in an oxygen tent from the outset with an ambient oxygen concentration of 40-60 per cent. The temperature was lowered by tepid sponging. She was treated with penicillin, ampicillin and cloxacillin and digitalised in an attempt to control her tachycardia. A generalised convulsion several hours after

admission was controlled with phenobarbitone. Within 24 hours her temperature had fallen to 38°C with improvement in her general condition. Her temperature remained elevated, 37-39°C, during the next two weeks, however, and serial X-rays showed an increasing right pleural effusion and patchy consolidation of both lung fields. 15 ml of greenish fluid was aspirated from the right side of the chest on the seventh day but was found to be sterile. Subsequent clinical and radiological improvement was gradual, and antibiotics were stopped after five weeks. Chest X-ray showed considerable resolution at that time, but six months elapsed before appearances were normal.

DISCUSSION

The disturbances of blood gas tensions and pH in these infants resulted from extensive parenchymal lung disease, often accompanied by mechanical complications impairing ventilatory efficiency. A plan for the management of such cases, based on extensive experience in a specially equipped intensive care unit, has been outlined by Jones et al. (1968).

The maintenance of a clear airway was a major problem in the patients described, and could not be achieved with nasal and pharyngeal suction alone. Repeated tracheo-bronchial suction through a naso-tracheal or tracheostomy tube (Bush, 1966) combined with measures to correct ventilatory insufficiency were required. Cases 1-3 may have fared better had they received ventilatory assistance from the outset, with more adequate measures to prevent and correct pleural complications. An aggressive surgical approach to empyema (Groff et al., 1966) may also have helped in Cases 1 and 2, as both had large empyema at autopsy.

When a broncho-pulmonary fistula develops as in Case 2 (see Table 18) however, the technical problems of assisted ventilation are exceedingly difficult to overcome (Fisk, 1966).

Hypothermia often accompanies staphylococcal pneumonia in infancy, and when severe is of grave prognostic significance. The isolation of antibiotic-sensitive organisms from empyema fluid at autopsy (Case 1) suggests that antibiotic therapy in conventional dosage was ineffective. Antibiotics had been given intramuscularly into areas of buttock or thigh of lard-like consistency, which raises the question of their absorption and utilisation by this route when severe hypothermia is present.

The need for a high ambient oxygen concentration to maintain an adequate Po_2 in these infants, reflects severe ventilation/perfusion imbalance and probably right to left shunting of blood through atelectatic or consolidated lung tissue. The importance of hypoventilation as a mechanism of hypoxaemia is indicated by the high Pco_2 values obtained. Inappropriate ventilation/perfusion ratios are likely to be the cause of persistent hypoxaemia when Pco_2 has returned to normal (Case 5, Table 19).

The acid-base disturbances confirm the findings of Stevens et al. (1965) who reported serial acid-base observations in nine infants with staphylococcal pneumonia. These authors emphasised the frequent occurrence of respiratory acidosis, often well compensated, and the rapid changes which can occur in relation to the development, correction or recovery from the various mechanical complications which impair ventilation. Blood gas tensions and pH may change remarkably quickly in these circumstances, and isolated measurements are of limited clinical or prognostic value. In the present series, however, none of the patients with severe ventilatory failure survived.

SUMMARY

The changes in arterial blood gas tensions and pH in five infants with staphylococcal pneumonia are described. Severe hypoxaemia and carbon dioxide retention were the main abnormalities found in these patients. 40 per cent oxygen did not always relieve hypoxaemia, and in two infants a normal Po_2 was not attained in 50-70 per cent oxygen.

The blood gas disturbances were related not only to the severity of pneumonia and degree of pulmonary involvement, but also to the occurrence of mechanical complications during the course of the illness. Frequent monitoring of blood gas tensions and pH, the early recognition of complications and an aggressive approach to management offer hope for reducing mortality in the future.

S E C T I O N III

Chapter 1

ACUTE ASTHMA

ARTERIAL BLOOD GAS TENSIONS AND pH IN ACUTE ASTHMA IN CHILDHOOD

INTRODUCTION

The arterial blood gas tensions in bronchial asthma in adults have been the subject of several recent reports (Rees, 1966; Waddell et al., 1967; Tai and Read, 1967; Palmer and Diament, 1967; McFadden and Lyons, 1968). The situation in childhood asthma is not so well studied despite the evidence that respiratory failure is not uncommon (Tsuchiya and Bukantz, 1965; Downes and Wood, 1965) and death by no means rare in status asthmaticus in children (Lanoff and Crawford, 1964; Richards and Patrick, 1965). In addition, there has been the increase in mortality from asthma at all ages, most pronounced at ages 10-14 years (Speizer et al., 1968), and attributed to the increased use of pressurised aerosols containing isoprenaline (Speizer et al., 1968; Innan and Adelstein, 1969).

In severe asthma in adults respiratory acidosis may be aggravated by injudicious oxygen therapy (Schiller et al., 1951), but the importance of this potential danger in children with severe acute asthma is uncertain. The clinical features and arterial blood gas findings in 21 children studied during 24 acute exacerbations of asthma are reported, and the response to therapy, in particular the administration of oxygen or sodium bicarbonate is described. These findings have been reported previously (Simpson, Forfar and Grubb, 1968). Here, a detailed account of the effects of treatment with oxygen, sodium bicarbonate, and inhalational ether is presented.

PATIENTS

The patients (12 males and 9 females) ranged in age from 2 to 12 years and were admitted to the Royal Hospital for Sick Children, Edinburgh, between September 1965 and December 1967. Clinical details on admission are summarised in Table 20. A personal or family history of asthma or allergy was obtained in 19 patients. No such history was elicited in Cases 1 and 21. Case 1 was studied on two separate admissions and Case 2 on three. The severity of asthma was graded according to the classification of Kraepelein et al., (1958), grade I consisting of five attacks per year, grade II of five to ten attacks per year, and grade III of ten or more attacks or the presence of continuous symptoms. All grade III cases in this study had been on continuous steroid therapy for one to three years. Each child had moderate to severe respiratory distress with recession of the supra-clavicular spaces, intercostal spaces, and costal margins during inspiration. Several of the children were restless and others were very drowsy. On auscultation the breath sounds were diminished, with prolonged expiration, and were accompanied by rales and rhonchi. Chest x-ray films showed overinflation and hypertranslucency in all cases, but in Cases 1b, 6, 9, 11, and 15 there were also zones of collapse or consolidation.

PLAN OF INVESTIGATION

Each case was assessed clinically soon after admission to hospital. Respiration and pulse rates were counted for one minute before arterial sampling, and cyanosis of the lips was assessed as present or absent by two independent observers. All equivocal observations were classed

as "cyanosis absent". Lighting conditions were not uniform, as the children were studied at different times of night and day. Any restlessness or impairment of consciousness was noted. Blood samples were taken after the child had been breathing air or one constant oxygen concentration for at least 20 minutes. Arterial blood was then obtained.

Oxygen was administered in an Oxygenaire Universal Tent at a flow rate of 4-10 litres per minute and the patient was positioned with one limb extruded from the tent to facilitate arterial sampling without opening the tent. Four to six samples of inspired gas were taken during the 20 minutes before and during blood sampling. The mean values of the oxygen concentrations of these samples (FIO_2) are given in Table 21. Individual samples were within the range mean value $\pm$3% on all occasions but one (Case 7). After the initial period of air-breathing, oxygen was administered and subsequent blood and gas samples were taken as determined by clinical progress. In most cases therapy also included adrenaline hydrochloride 1:1,000 0.2-0.5 ml. subcutaneously and prednisolone 40 mg/day irrespective of body weight (see Table 20). Cases 1a, 1b, 2a, and 2c were also given 100 mg of hydrocortisone intravenously every two hours during the acute phase of their illnesses. Sedation was avoided in most cases. All cases were treated with antibiotics, the majority being given ampicillin 50 mg/kg/day. Dehydration was corrected by oral or intravenous fluid therapy, and 8.4% sodium bicarbonate was administered intravenously in Cases 1a, 1b, 2a, 2c, 4, 5, and 8 to 'defend' a falling pH, and possibly restore responsiveness to adrenaline. Intermittent positive pressure respiration and inhalational ether were used in the treatment of Cases 1a, 1b, 2a and 2c.

RESULTS

All 21 patients in the present series recovered. Case 18 recovered but died at home some months later during a severe bout of asthma. Necropsy was not carried out and no details are known. Their arterial blood gas tensions, pH, and calculated data on admission to hospital are shown in Table 21. The arterial Po_2 was below 75 mm Hg in all cases breathing air and in four it was less than 50 mm Hg. Carbon dioxide retention, with a Pco_2 of 50 mm Hg or over, was present in ten admissions (six breathing air, four breathing oxygen), but in Case 14 the Pco_2 was 26 mm Hg. pH ranged from 7.05 to 7.46 and was below normal (< 7.36) in eleven admissions. The acid-base findings in the twenty children studied initially in air are summarised in Table 21a.

On admission the respiration and pulse rate of patients breathing air did not correlate with either arterial Po_2 ($P=0.9$) or Pco_2 ($P=0.9$). Cyanosis was noted on nineteen occasions (admission and follow-up assessments). In all but one the arterial So_2 was less than 90% and in fourteen, less than 85%. When cyanosis was absent the So_2 was always over 85%, being over 90% on all but four occasions. The mean arterial Po_2 in the seven patients who were restless when breathing air on admission, was significantly lower than the Po_2 in those who were not breathless at this time ($P< 0.05$). Restlessness, however was not a reliable guide to the Po_2 when assessments were made with the patients breathing oxygen.

Drowsiness and confusion proved difficult to assess, particularly in the younger patients in the series, and precise correlation with either Po_2 or Pco_2 was not possible. Cases 1b, 4, 5 and 14, however, became very drowsy at a stage when their respective Pco_2 levels were 85, 72, 80 and 26 mm Hg, and when in each the Po_2 exceeded 70 mm Hg.

Effects of Treatment

Details of treatment are summarised in Table 20. Adrenaline was given to 18 patients. The pH was below normal in nine of the 14 in whom the response to adrenaline was unsatisfactory. In four patients who responded satisfactorily, the pH was within normal limits (7.36-7.42). In Cases 1a, 1b, 2a, 2c, 4, 5, and 8, sodium bicarbonate was infused. Large doses were required to maintain a pH >7.20 in Cases 2a and 2c before assisted ventilation.

Carbon dioxide retention increased in Cases 1a, 1b, 2a, 4, 5, 8 and 10, during the course of treatment, and Cases 1a, 2a and 2c became unconscious while breathing oxygen. The time course of changes in blood gas tensions in relation to treatment of Cases 1a, 1b, 2a and 2c (in whom manual ventilation and inhalational ether were also employed) is described in Section III, Chapter 2. The time course of events in Cases 4, 5 and 8 is illustrated in Figures 11, 12 and 13. In Case 10 the Pco_2 rose from 46 to 57 mm Hg while breathing oxygen, and pH fell from 7.36 to 7.30. No further measurements were made in this patient who recovered uneventfully.

After clinical recovery a normal acid-base status was restored in all cases within one to three days, but hypoxaemia in air often persisted for seven to ten days (Figure 14).

ILLUSTRATIVE CASE REPORTS

Case 4 This five-year-old boy developed a cough and wheeziness some 48 hours prior to his admission to hospital. His symptoms were thought to have been precipitated by contact with a dog. On the day of admission he had become progressively more breathless, and had used an isoprenaline medihaler on several occasions. His family doctor noticed that he was

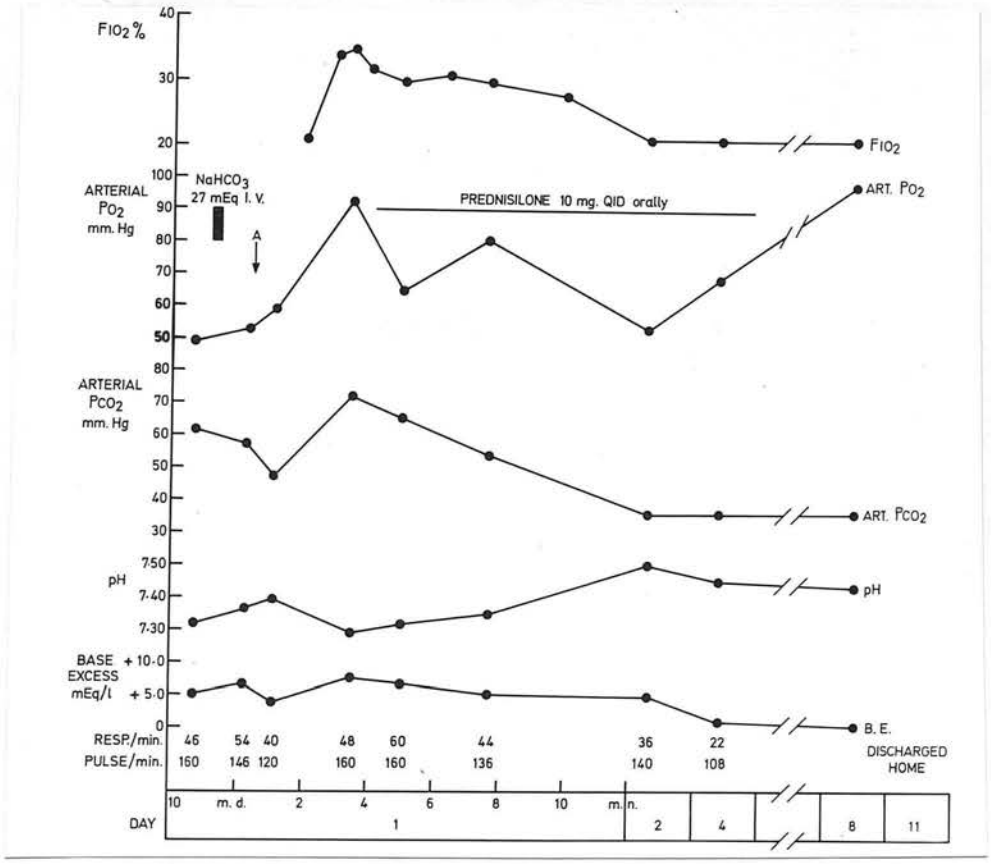

Figure 11

Time course of changes in acid-base variables with treatment (Case 4) Following the administration of sodium bicarbonate (2 mEq/Kg) the increase in pH is accompanied by a fall in Pco_2. This trend is reversed with the administration of oxygen.

A: Adrenaline

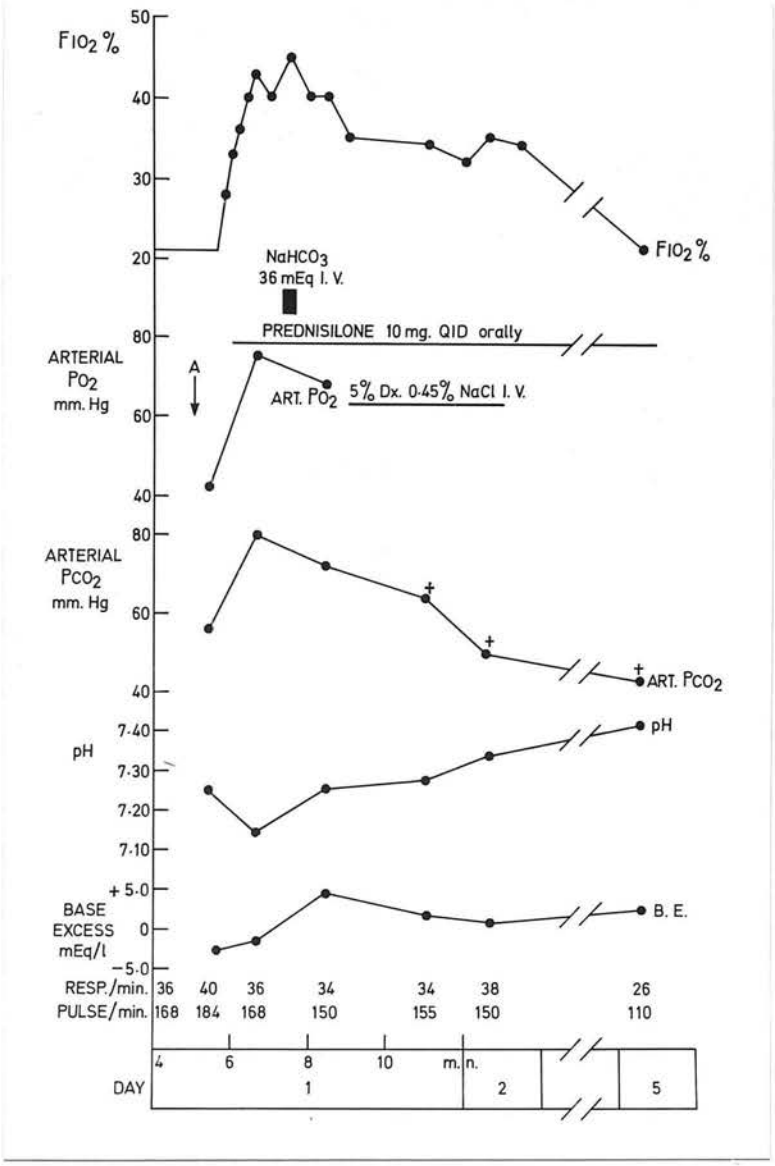

Figure 12

Effects of oxygen therapy and infusion of sodium bicarbonate (2 mEq/Kg) on blood gas tensions and pH (Case 5). A rise in Pco_2 and decrease in pH follow the administration of oxygen. Infusion of alkali and the simultaneous reduction in inspired oxygen concentration is succeeded by a rise in pH and fall in Pco_2.

+ Capillary blood sample A: Adrenaline

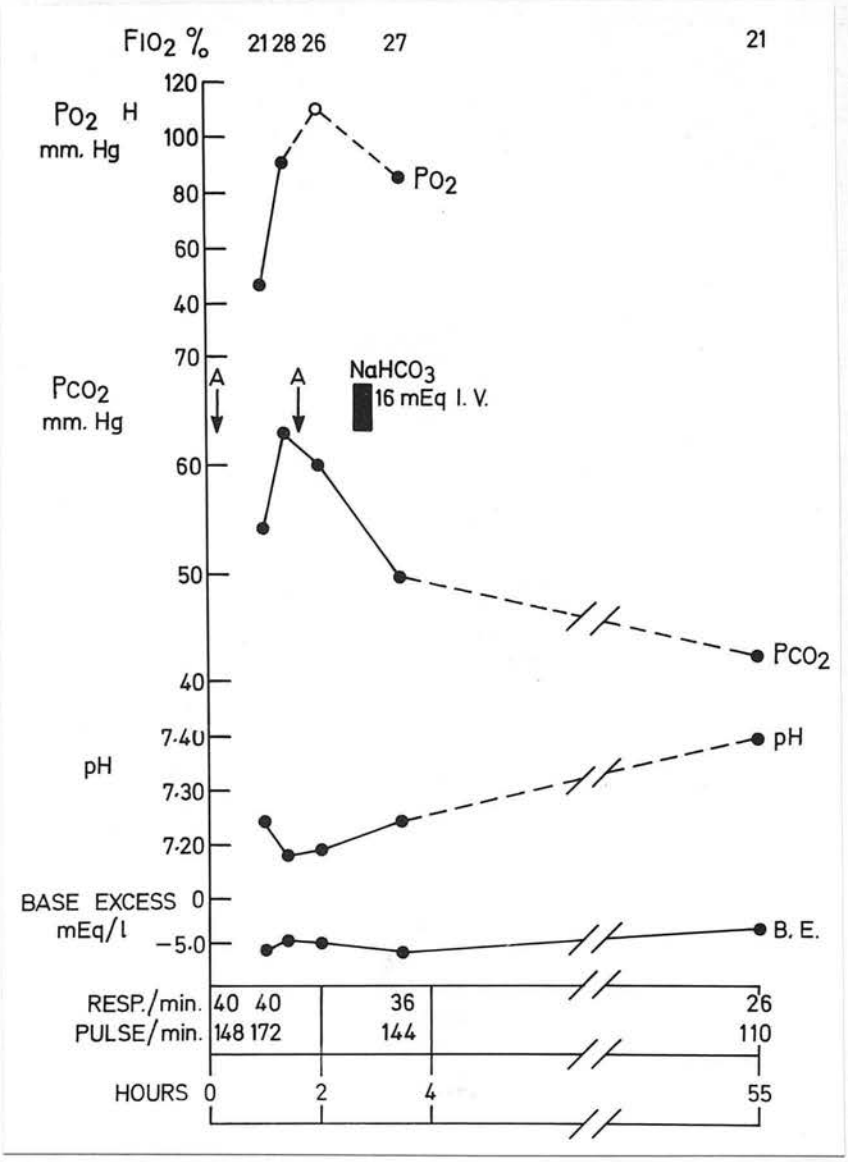

Figure 13

Effects of treatment on acid-base variables (Case 8). Pco_2 increases and pH decreases following the administration of oxygen. An increase in pH and reduction in Pco_2 follow the infusion of sodium bicarbonate (1 mEq/Kg).

A: Adrenaline

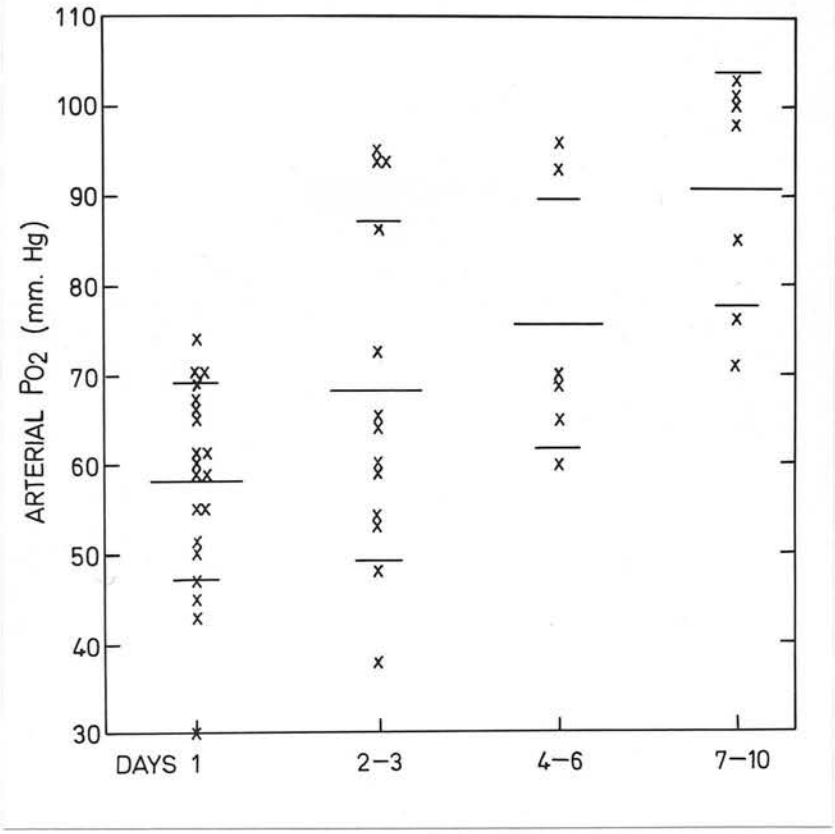

Figure 14

Mean arterial Po_2 levels ($\pm$ 1 S.D.) in patients breathing air up to ten days after admission.

cyanosed in air and had treated him with subcutaneous adrenaline, with little effect. During the preceding year he had had recurrent episodes of wheeziness, following an acute lower respiratory tract infection. There was no definite family history of allergy, or personal history of eczema or food allergy.

On examination he was a slender child who was wheezing and dyspneoic. Alae nasae were flaring, the chest was held in the inspiratory position, and there was marked subcostal and intercostal recession. Percussion note was hyperresonant and breath sounds diminished vesicular, accompanied by high pitched rhonchi throughout both lung fields. Crepitations were audible at the right lung base. Plate VIII shows X-ray appearances.

The changes in blood gas tensions and pH during the course of his illness are shown in Figure 11. He was in ventilatory failure at the outset, with a Pco_2 of 61 mm Hg. Sodium bicarbonate was infused in the hope of restoring responsiveness to adrenaline. Adrenaline 1:1000 0.3 mls was then administered subcutaneously with immediate, but short-lasting, relief of bronchospasm. He was then transferred to an oxygen tent. Symptoms gradually worsened, and some two hours following the administration of adrenaline (within an hour of starting oxygen therapy) Pco_2 had risen to 72 mm Hg, and pH had fallen to 7.29. An attempt was made to maintain the inspired oxygen concentration at approximately 30 per cent thereafter, and treatment with prednisolone 10 mgm QID was started. He improved gradually and Pco_2 fell to 36 mm Hg within the following twelve hours. Arterial Po_2 did not return to a normal level for seven days. He was discharged home on the tenth day following admission.

Case 5 This five-year-old girl was admitted to hospital with a thirty hour history of wheeze and increasing breathlessness. She had become

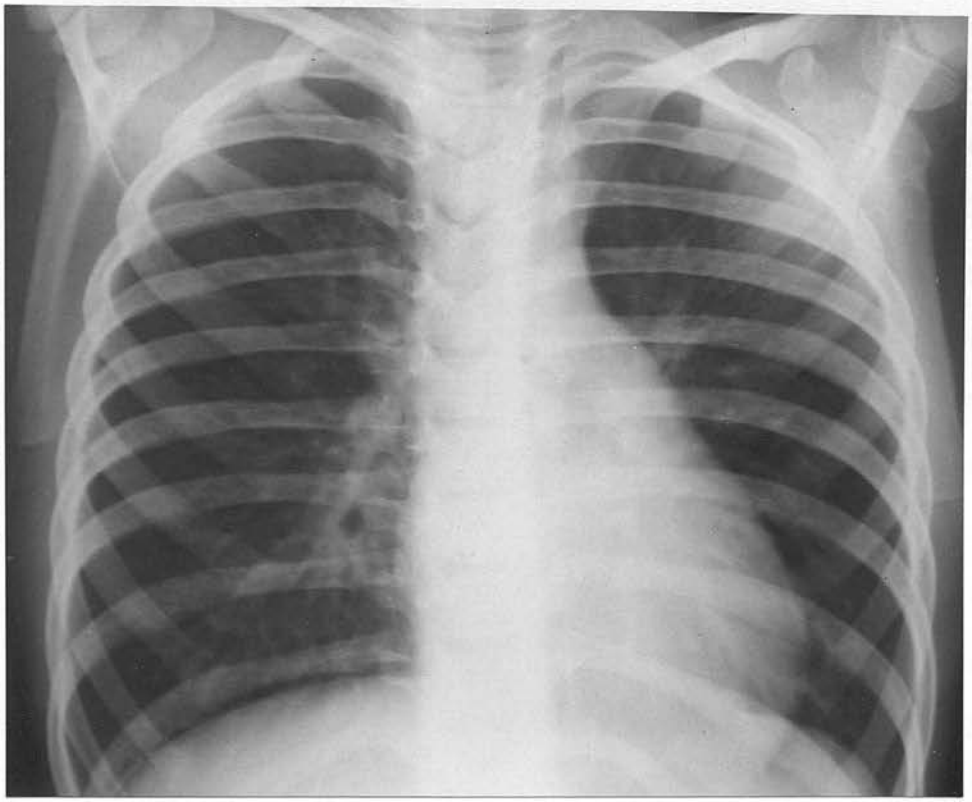

Plate VIII

Severe Acute Asthma: Chest X-ray on admission - Case 4

restless and anxious and was noted to be sweating profusely and blue around the mouth. She vomited on two occasions. She had a long history of recurrent wheeziness, starting when she was 18 months old, and preceded by eczema during the first year of life.

On examination she was pale and cyanosed with severe respiratory distress. She was sweating and febrile (temperature 37.6°C). There was marked indrawing of the supraclavicular tissues and intercostal spaces. Percussion note was hyperresonant. Breath sounds were harsh vesicular with prolonged expirations, and accompanied by generalised expiratory rhonchi. Plate IX shows X-ray appearances.

The time course of changes in acid-base variables in relation to therapy is shown in Figure 12. Subcutaneous adrenaline 1:1000 0.2 mls given on admission, produced little improvement, and she was found to have severe respiratory acidosis with a Pco_2 of 56 mm Hg and pH of 7.25. Prednisolone 10 mgm QDS was started orally and hydrocortisone 50 mgm intravenously given at the outset. She was transferred immediately to an oxygen tent and soon after was pink but somewhat drowsy. Pco_2 had risen to 80 mm Hg and pH had fallen to 7.14. Sodium bicarbonate was infused while preparations were made to assist ventilation. Two hours later Pco_2 was 72 mm Hg and pH 7.25. She was less distressed than previously, but still drowsy. It was decided to persevere with conservative treatment and to try to maintain the inspired oxygen concentration near 30 per cent. She improved gradually thereafter, and acute symptoms subsided within 24 hours. She was discharged from hospital several days later.

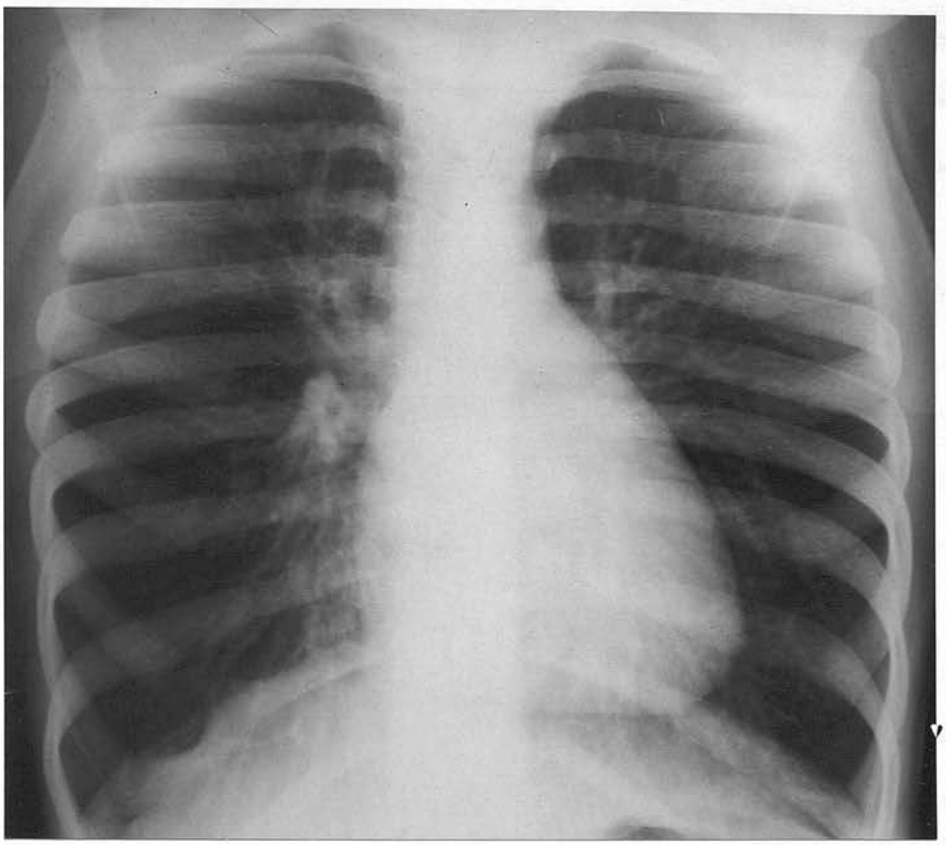

Plate IX

Severe Acute Asthma: Chest X-ray on admission - Case 5

Case 8 This eight-year-old child was admitted to hospital with increasing wheeze and dyspnoea of 36 hours duration. On the day of admission she had used an isoprenaline aerosol on two occasions and had vomited tablets prescribed by the family doctor. She had been having recurrent attacks of bronchospasm since the second year of life, and was known to become wheezy on contact with dogs. There was a family history of asthma and hay fever.

On examination she was anxious and distressed with a loud wheeze and laboured respirations. Overdistension of the chest, indrawing on inspiration and generalised expiratory rhonchi were all present at the outset. Plate X shows X-ray appearances.

Adrenaline 1:1000 0.5 mls was administered subcutaneously on admission, but two hours later there was no obvious improvement. Arterial blood gas tension and pH on admission and following treatment are shown in Figure 13. Her arterial Pco_2 at that time was 54 mm Hg and pH 7.22 breathing air. She was then treated in an oxygen tent with 26-30 per cent oxygen (the potential hazard of oxygen therapy was suspected and the inspired oxygen concentration was limited to 30 per cent or less). Severe symptoms persisted with Pco_2 rising to 63 mm Hg and pH falling to 7.18. Adrenaline was again administered without obvious improvement. Sodium bicarbonate was then infused and was followed by gradual clinical improvement. Within an hour Pco_2 had fallen to 49 mm Hg and pH had risen to 7.24. She improved steadily thereafter, and was finally discharged home after five days.

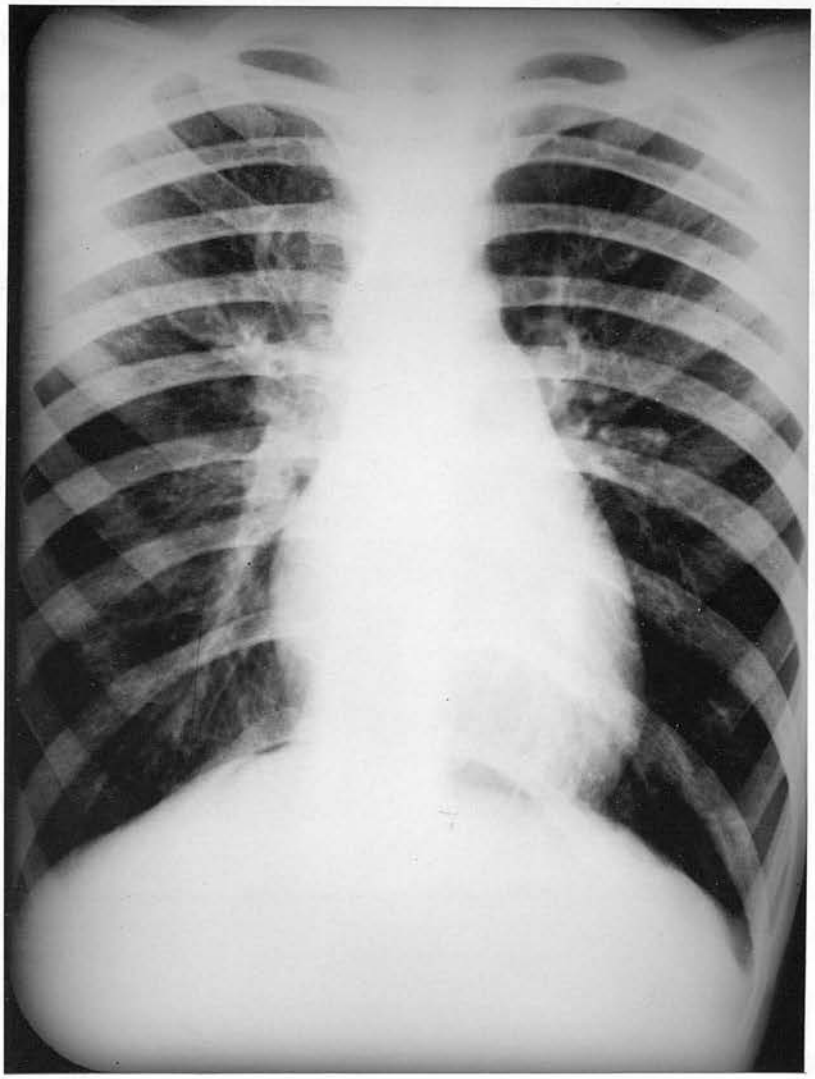

Plate X

Severe Acute Asthma: Chest X-ray on admission - Case 8

DISCUSSION

These results confirm the findings of Downes et al. (1966) that hypoxaemia and respiratory acidosis are not uncommon in acute asthmatic attacks in childhood. In addition, this study allows an assessment of the clinical signs of hypoxaemia and carbon dioxide retention, and of the effects of oxygen and bicarbonate therapy.

Correlation with Clinical Features

The severity of hypoxia and hypercapnia in these children was unrelated to the grade of severity of asthma as determined by the classification of Kraepelien et al. (1958), or to the duration of acute symptoms. Case 1a had previously had only one mild asthmatic attack. Case 2a, a child with chronic asthma on long-term steroid therapy, developed severe respiratory failure (Table 21) within two hours of the onset of symptoms.

A raised respiration rate and tachycardia could result from multiple causes in these patients. It is not surprising, therefore, that these indices did not correlate with Po_2 measurements. Severe hypoxaemia may occasionally be present without cyanosis, but cyanosis, when present, was a reliable sign of hypoxia, all cases being cyanosed when the So_2 was below 85%. Restlessness was a useful sign of hypoxia in patients breathing air, but was not of value in patients breathing oxygen. Perhaps claustrophobic effects accounted for the agitation and restlessness occasionally present in oxygen tents when hypoxaemia had been relieved. Carbon dioxide narcosis abolished restlessness completely.

Though patients with hypercapnia are often very drowsy, Case 14 with a Pco_2 level of 26 mm Hg, was confused and difficult to rouse at first, presumably because of the combined central effects of hypoxia

hypocapnia, and previous sedation. This patient was not clinically different from many others in the series with hypercapnia. Loss of consciousness, noted in Cases 1a, 2a, and 2c, during oxygen therapy must be regarded as due to severe carbon dioxide retention demanding immediate treatment. The danger of sedation in producing respiratory depression has been emphasised by Neder et al. (1963), and it is noteworthy that several patients with marked carbon dioxide retention in the present series, had been sedated before the initial study (Tables 20 and 21).

Of the clinical signs discussed, therefore, cyanosis was of most value as a guide to the arterial So_2, while there were no really reliable guides to the Pco_2 level, an experience similar to that of Bates and Christie (1964) in adults.

Hypoxia and its Mechanisms

The importance of disturbed ventilation-perfusion ratios in the lungs as a mechanism of hypoxaemia in asthma has been shown by several studies in children (Ledbetter et al., 1964; Lecks et al., 1965). In a study of ten patients under the age of 35 during acute attacks of bronchospasm, McFadden and Lyons (1968) showed that uneven ventilation may persist even when total airway resistance measured by conventional methods is brought under control by treatment. The increased $A\text{-}aDo_2$ values (normal 10 mm Hg) in patients breathing air (Table 21a) probably reflected such ventilation-perfusion imbalance. This persisted for some time after clinical recovery, as the arterial Po_2 was often below normal for seven to ten days (Figure 14) despite the fact that the Pco_2 was generally normal within 48 hours. There was a significant correlation

(P=0.001) between arterial Po_2 and Pco_2 in cases breathing air on admission (Figure 15) which suggests that alveolar hypoventilation is also important as a mechanism of hypoxaemia in the acutely ill asthmatic child.

Hypercapnia and Acid-Base Balance

Feldman (1962) emphasised the grave prognostic significance of an increase in arterial Pco_2 in adults with severe asthma, and in no fewer than 10 of 24 admissions the Pco_2 was 50 mm Hg or above (Table 21) This confirms previous observations that ventilatory failure is not uncommon in severe acute asthma in children (Tsuchiya and Bukantz, 1965; Downes et al., 1966) and contrasts with the usual findings in adults. Rees (1966) found that carbon dioxide retention was uncommon in his 24 adult patients in status asthmaticus and that one-third were hyperventilating with a Pco_2 level below 35 mm Hg. On the other hand, Tai and Read (1967) found that in 8 out of 12 adult cases, most of whom were breathing oxygen at the time, Pco_2 levels were greater than 50 mm Hg on admission to hospital. Only one patient in the present series (Case 14, Pco_2 26 mm Hg) was hyperventilating initially, but could not be distinguished clinically from other children in the series.

An association between a low pH and an unsatisfactory response to adrenaline was noted in our patients. Blumenthal et al. (1961) postulated that asthmatics become adrenaline-resistant because of respiratory acidosis and found that responsiveness to adrenaline was restored in some patients after infusions of alkali. Turiaf et al. (1962) and Tsuchiya and Bukantz (1965) showed, however, that there is no constant relation between adrenaline resistance and acidosis, though severely acidotic patients invariably fail to respond to adrenaline. Tenney (1956) has

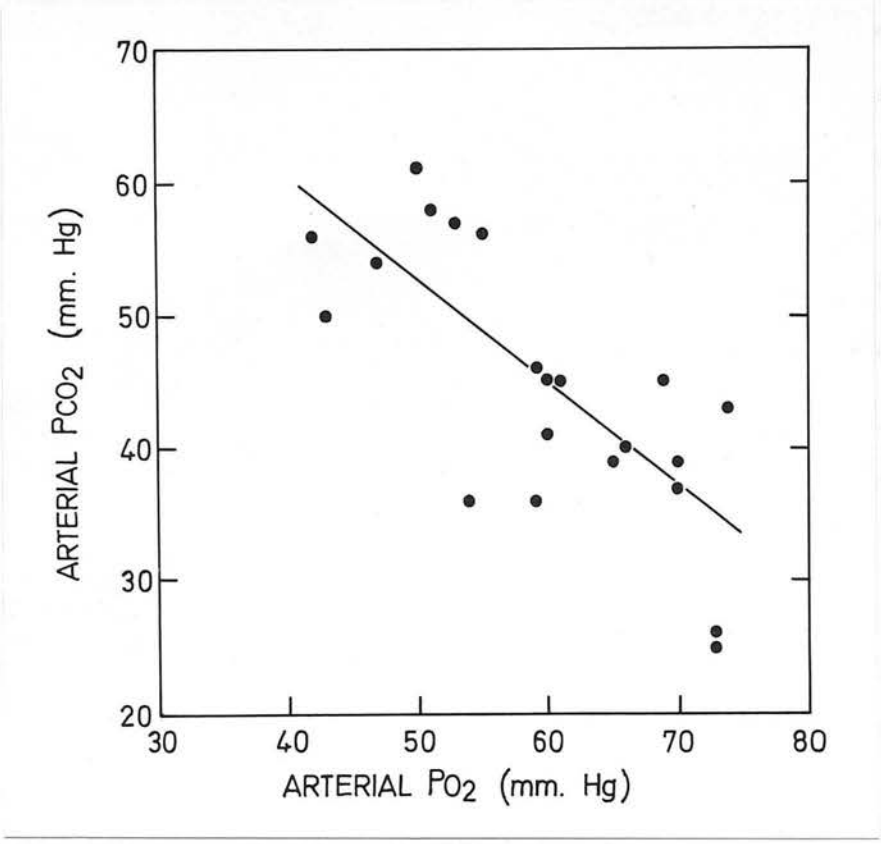

Figure 15

Relation between arterial Po_2 and Pco_2 on admission, when breathing air.

$$Pco_2 \text{ mm Hg} = -0.79\ Po_2 \text{ mm Hg} + 93$$

$$r = -0.75\ ;\ P < 0.001$$

suggested that this apparent inhibition of response to adrenaline may be due to an increase in circulating pressor substance caused by the rise in the Pco_2.

Simpson, Grubb and Forfar (1968) reported moderate metabolic acidosis in several of their patients, based on negative values of base excess outwith the normal range. Correction of their base excess values for the in vivo effect of carbon dioxide however, shows that only 3 patients, (Cases 2b, 8 and 14) had significant metabolic acidosis. Sodium bicarbonate administration was not therefore indicated for the correction of metabolic acidosis as stated by these authors, but was nevertheless a valid treatment in view of previous reports on its use, (Blumenthal, 1961; Mithoefer, 1965). It is difficult to dissociate the effects of sodium bicarbonate from that of other treatment. The dramatic clinical and blood gas improvement noted by Mithoefer (1965) following the administration of sodium bicarbonate to adults in severe respiratory failure due to asthma, was not observed in these children. In Cases 4 and 8, Figures 11 and 13, however, sodium bicarbonate was administered without a concomitant change in inspired oxygen concentration - in both cases an increase in pH was associated with a decrease in Pco_2. The use of sodium bicarbonate in Cases 1a, 1b, 2a and 2c is described in Section III, Chapter 2, p. 62.

Cases 3, 4, 11, and 15 showed increasing metabolic alkalosis for one to two days after admission, though none of them had been given parenteral bicarbonate. This renal reabsorption of bicarbonate is an important defence against respiratory acidosis in adults (Refsum, 1964) and in children with acute lower respiratory tract infections (Simpson and Flenley, 1967), but it is too slow a mechanism to be of great importance in acute asthma, where dangerous hypercapnia may develop very rapidly.

The significance of arterial blood lactate and pyruvate concentrations, determined in Cases 1b, 2a, 2b, 2c, 5, 10-12 and 19-20 is discussed in Section VI.

Effects of Oxygen Therapy

Oxygen was given to all acutely ill children on admission, and was assumed to be adequate when the arterial Po_2 rose to 80 mm Hg or more. In Figure 16 the arterial Po_2 is plotted against the FIo_2 at the time when arterial blood samples were taken - all data being obtained in the first 24 hours after admission to hospital. This shows that oxygen therapy in the 25-40% concentration range may fail to relieve hypoxia in many cases. On four occasions (Cases 1a, 2c, and 5) an oxygen concentration of 40% or more did not ensure a normal Po_2, which supports the findings of Downes and Wood (1965), who suggest, however, that an inspired oxygen concentration of 50-60% should be used in the routine conservative treatment of acute asthma. Unfortunately, the uncontrolled use of oxygen may precipitate carbon dioxide narcosis (see below), and controlled oxygen therapy in the 25-30% concentration range, designed to correct hypoxia partially and to minimise further carbon dioxide retention, may be more appropriate in certain cases. However, precise control of the inspired oxygen concentration over a prolonged period cannot be achieved in oxygen tents in current paediatric use (Simpson and Russell, 1967), and masks used for this purpose in adults are not well tolerated by children.

Carbon Dioxide Narcosis

An increase in Pco_2 during oxygen therapy is a recognised danger in treating respiratory failure in the adult asthmatic (Schiller et al.

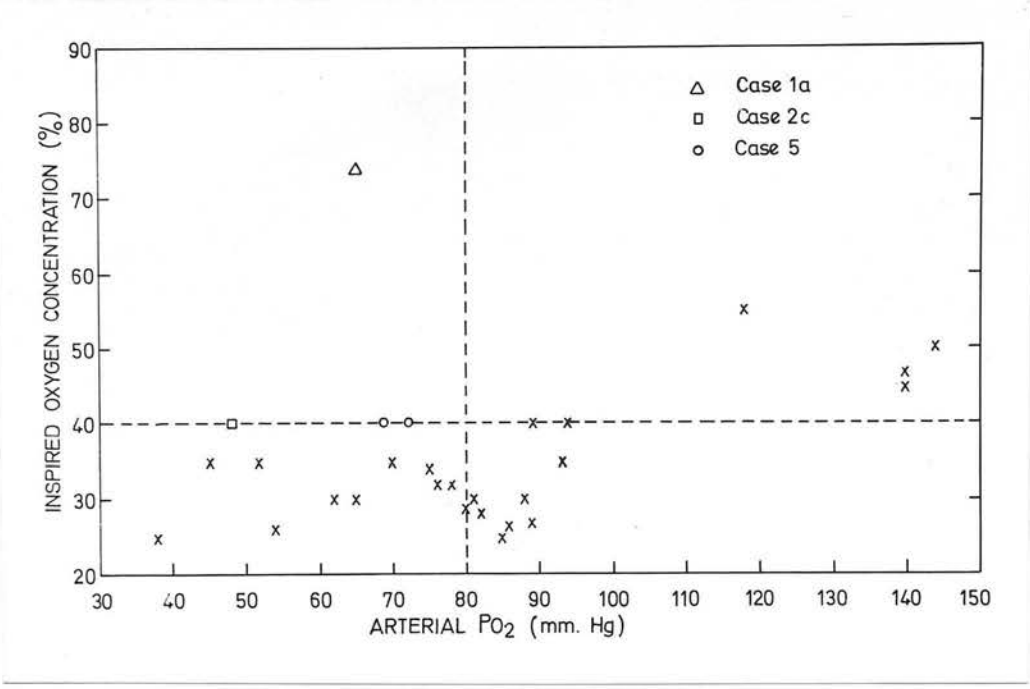

Figure 16

Arterial Po_2 at various levels of inspired oxygen concentrations. In Cases 1a, 2c and 5 an inspired oxygen concentration of 40 per cent did not produce a Po_2 of more than 80 mm Hg.

1951). Downes and Wood (1965), however, found that the administration of 100% oxygen to seven children in status asthmaticus did not produce a rise in Pco_2. The actual Pco_2 levels in these cases were not stated. In this series the Pco_2 was 50 mm Hg or above in ten admissions (six breathing air and four oxygen) and oxygen therapy or further oxygen therapy did produce a rise in Pco_2. This is illustrated in Figure 17, where Po_2 is plotted against Pco_2 in the same patient, both at the time of admission and within three hours of beginning oxygen therapy. (Figures 11, 12 and 13 show the precise sequence of events in Cases 4, 5 and 8). As the Po_2 increased with oxygen therapy, the Pco_2 rose in all but one patient (Case 9, Pco_2 50 mm Hg). Previous infusion of sodium bicarbonate may have influenced the Pco_2 response in Case 1a. In normal adults a small rise in Pco_2 may follow the infusion of sodium bicarbonate (Katsaros et al., 1960), but Mithoefer et al., (1965) reported a fall in Pco_2 in six hypercapniac asthmatics soon after bicarbonate infusion. A fall in Pco_2 following the use of (THAM) in two children with status asthmaticus has also been described (Strauss et al., 1966). Case 2a had been sedated with phenobarbitone and paraldehyde before being studied in either air or oxygen, which almost certainly contributed to the severity of her respiratory depression.

CONCLUSION

As clinical signs relate poorly to dangerous degrees of hypoxaemia and hypercapnia in acute asthma in childhood, it is important to measure the arterial blood gas tensions in all severely ill asthmatic children. Serial estimations of Pco_2 in particular are essential during oxygen therapy in view of the risk of aggravating respiratory acidosis.

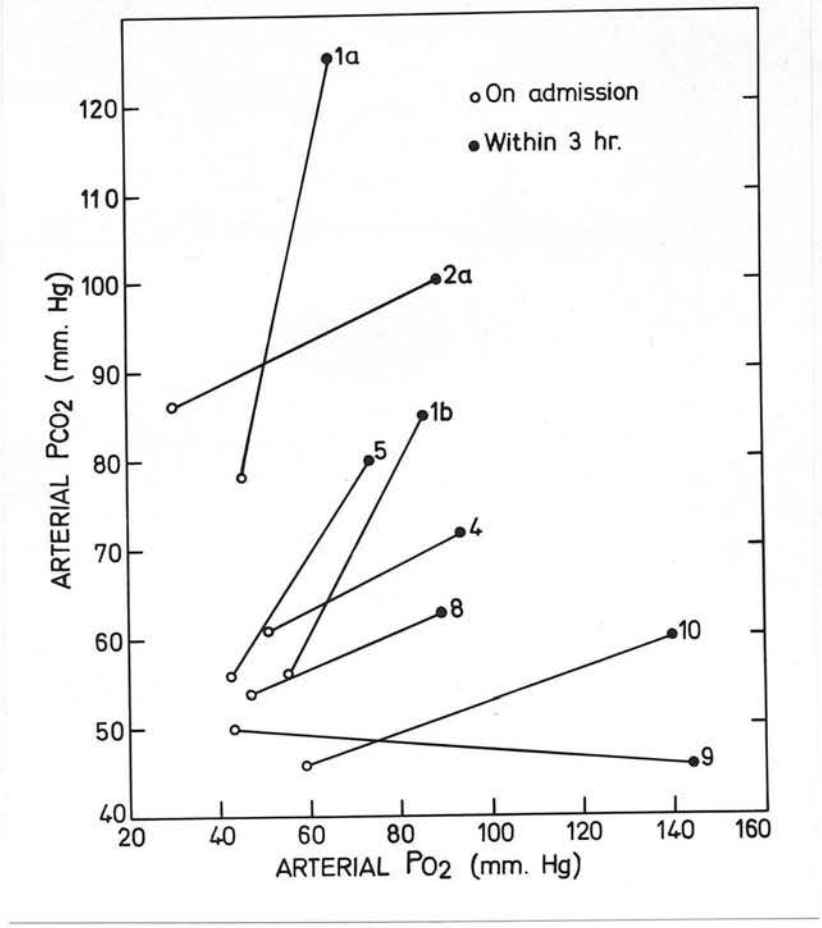

Figure 17

Changes in arterial Po_2 and Pco_2 after oxygen in the first three hours.

To ensure greater accuracy the observations were all made on arterial rather than arterialized capillary blood. In routine practice, however, capillary blood measurements, though less precise, might sometimes be more appropriate and could obviate the need for repeated arterial punctures when frequent blood samples became necessary.

SUMMARY

Studies of the arterial blood gas tensions and pH in 21 children during twenty-four acute attacks of asthma showed that all were hypoxic on admission to hospital, and in ten there was evidence of carbon dioxide retention. Cyanosis, invariably present when the So_2 was below 85%, and restlessness in patients breathing air, were the most reliable clinical guides to the Pco_2 levels. Conventional oxygen therapy in tents(25-40%) did not always relieve hypoxia, and in three cases the administration of oxygen at a concentration of 40% or over failed to produce a normal arterial oxygen tension. Uncontrolled oxygen therapy may aggravate respiratory acidosis, and three patients developed carbon dioxide narcosis while breathing oxygen. The necessity for blood gas measurements in the management of severe acute asthma in childhood is emphasised.

S E C T I O N III

Chapter 2

SEVERE VENTILATORY FAILURE IN ASTHMA

INTRODUCTION

Acute respiratory insufficiency from bronchial asthma usually responds to treatment with sympathomimetic drugs, particularly adrenaline, or corticisteroids. A small number of cases do not respond satisfactorily however and various treatments have been suggested for this group of patients. The recommendations that have been made include larger than usual doses of adrenaline (Broom, 1961), the use of adrenaline intravenously (Kahn, 1930), ether by rectum (Maytum, 1931), general anaesthesia (Tausig et al., 1952) and intravenous aminophylline (Hermann and Aynesworth, 1937). The latter has not been used as widely in paediatric as in adult practice in recent years in view of its potential hazards (Soifer, 1957). In the past decade the use of alkalising agents (Blumenthal, 1961; Matell, 1965; Mithoefer, 1965, 1968; Strauss et al., 1966), intermittent positive pressure respiration (Swensson 1963; Beam et al., 1965; Downes et al., 1965; Richards et al., 1967) and bronchial lavage (Broom, 1961; Ramirez, R. et al., 1966, 1971) have all been advocated.

In the series of children with severe acute asthma described in Chapter 1, p 47, two patients (Cases 1 and 2) developed severe respiratory failure, each on two occasions. Their clinical progress and the changes in blood gas tension and pH which occurred with a regime of treatment incorporating several of the above-mentioned recommendations, is described here.

Clinical Summaries

A brief summary of each patient's illness up till the time of admission to hospital is given for Cases 1a, 1b, 2a, 2c (Table 20). Details of subsequent clinical progress and treatment are presented in Tables 22-25.

Case 1a

This 22 month old child was admitted to hospital with a 1-2 day history of cough, wheeze and progressive breathlessness. She had been adopted at the age of two months and had remained well during the first year of her life. Thereafter she developed recurrent bouts of wheeziness each time she had an upper respiratory tract infection. There were four such episodes in the six months preceding her admission, although only one had been serious enough to require treatment in hospital. Apart from colds, no other precipitating factors had been noted. There was no history of infantile eczema or food allergy.

On examination she weighed 13.2 Kg. She was irritable, restless and uncooperative. She wheezed audibly and was slightly cyanosed. Alae nasae were in action, the chest was overdistended and there was marked intercostal and supraclavicular indrawing. Percussion note was hyperresonant and expiratory rhonchi were audible throughout both lung fields. Examination of other systems revealed no abnormality. She was treated initially with subcutaneous adrenaline 1:1000 0.3 ml and ampicillin 125 mgm QID. She settled at first and was pink in her oxygen tent. She again became restless, however, and was sedated first with phenobarbitone and later with chloral hydrate. Blood gas tensions and pH were first determined twelve hours later, by which time she was extremely distressed and cyanosed in 35 per cent oxygen. Her subsequent progress is summarised in Table 22. Additional treatment included prednisolone 10 mgm QID orally and hydrocortisone, 100 mgm IV every two hours for twelve hours. Dehydration was corrected using 0.45 per cent NaCL 4.3 per cent dextrose.

Despite many worrying moments during the course of her treatment, this child survived and was discharged from hospital ten days later.

CASE 1b

This 2½ year old child was admitted to hospital with a 1-2 day history of wheeze and progressive breathlessness. A mild cough and running nose had been present for several days. During the preceding six months she had been managed at home and had been on Prednisolone 5 mgm daily (five days out of seven).

On examination she weighed 14.2 Kg. She was pale, sweating and afebrile. She wheezed loudly and her lips were slightly cyanosed. Hydration was judged to be satisfactory. Her chest was overinflated and moved symmetrically. Percussion note was hyperresonant. Medium and high pitched rhonchi were audible throughout both lung fields. No other signs were noted. BP 130/80 mm Hg. Chest x-ray showed possible inflammatory changes at the right lung base.

Adrenaline 1/1000 0.3 mls was administered subcutaneously with marked clinical improvement within fifteen minutes. She was treated in air initially and settled. Some hours later she again became restless and distressed and adrenaline was repeated without striking effect. Steroids were then used in full dosage. Initial studies were undertaken some thirteen to fourteen hours following admission to hospital. Subsequent progress is summarised in Table 23. She was discharged home, fully recovered, one week later.

CASE 2a

This 8 year old child was admitted to hospital for "assessment". She had suffered from asthma and eczema for several years and had been treated intermittently with Prednisolone on an out-patient basis. Despite being on 7.5 mgm Prednisolone daily, chronic wheeziness persisted and she was admitted to hospital on that account. At that time, she was

also being treated with Tedral bd, an aminophylline suppository nocte, and antibiotics. She had been treated in hospital on several occasions previously, and had been known to develop syncope following bouts of cough.

On examination she weighed 17.2 Kg. She was wheezing slightly, but was not distressed. Her skin was dry and eczematous. Mucous membranes were pink; and there was no finger clubbing or lymphadenopathy. The chest was moderately deformed, but there was no indrawing or asymmetry. Breath sounds were harsh vesicular, with occasional low pitched expiratory rhonchi bilaterally. No other signs were detected. Prednisolone 7.5 mgm/day was continued. The following day she was clinically well and ambulant. After a visit to the X-ray Department she became exceedingly breathless on return to the ward, after climbing three flights of stairs. She started to cough uncontrollably and became cyanosed and unconscious. She was thought to have had a convulsion and 5 ml paraldahyde was given by intramuscular injection. Her subsequent clinical progress is summarised in Table 24. Additional treatment included hydrocortisone 100 mgm intravenously every two hours for twelve hours, and Prednisolone 10 mgm QID orally. Prednisolone was gradually reduced during the following week and she was eventually discharged after two weeks to continue Prednisolone 5 mgm bd at home. Plate XI shows chest X-ray appearances on admission and one week later.

CASE 2c

This 8 year old child was admitted to hospital on account of increasing wheeziness of several days duration. On the day prior to admission she had been given Prednisolone 20 mgm orally and hydrocortisone 100 mgm intravenously on two occasions. In the preceding three months

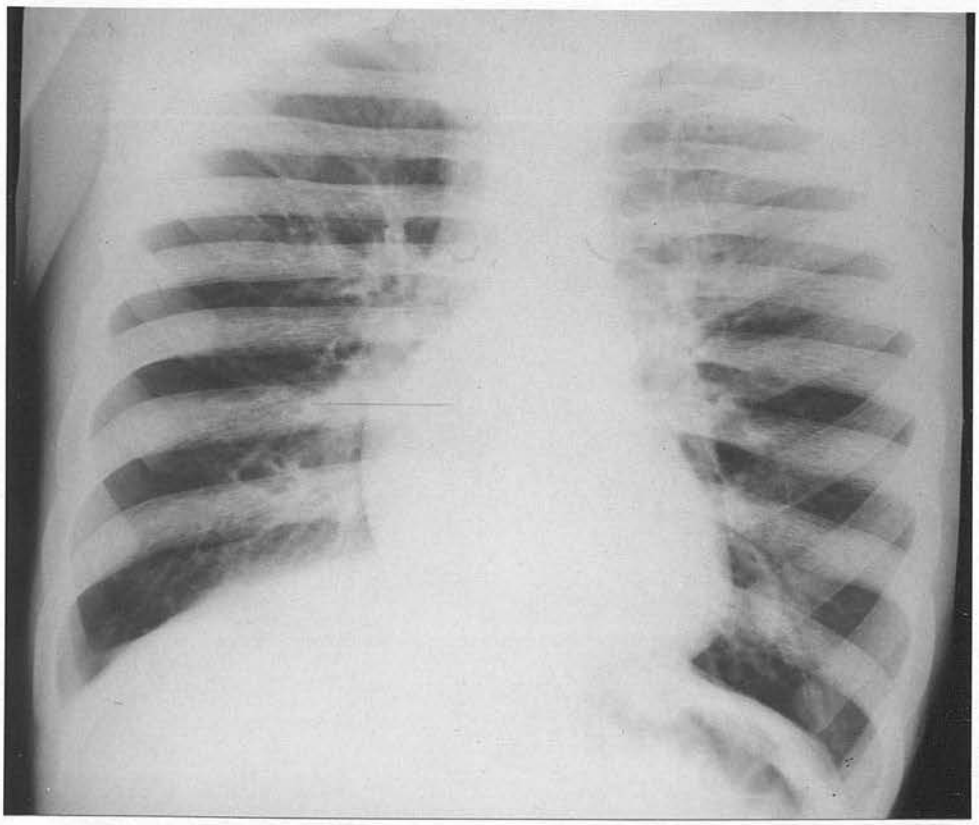

Plate XI

Severe ventilatory failure in asthma. Chest X-ray appearance

(Case 2a)

A: Day 1

Plate XI

Severe ventilatory failure in asthma. Chest X-ray appearance

(Case 2a)

B: After one week

her asthma had been well controlled with Prednisolone 5 mgm bd. She had been admitted to hospital on two occasions in the previous year.

On examination she weighed 18.0 Kg. She was wheezing, distressed and cyanosed. The accessory muscles of respiration were in use, and signs of severe bronchospasm were present. She had marked tachycardia, but no evidence of cardiac failure. Her B.P. was 95/70 mm Hg. No other signs were detected. At this stage arterial Po_2 was 60 mm Hg and Pco_2 45 mm Hg. Prednisolone was continued at 10 mgm QID and ampicillin 250 mgm QID was started. She was treated in an oxygen tent with 30-35 per cent humidified oxygen. She slept overnight, but in the morning she became very disturbed and cyanosed in oxygen. She became comatose within several minutes. Hydrocortisone, 100 mgm intravenously, was injected every two hours thereafter and an infusion of 0.45% NaCl 4.3% Dextrose was started. Her clinical course is shown in Table 25. On this occasion a muscle relaxant was used in association with intermittent positive pressure respiration. She was well and ambulant within a few days and was discharged home a week later to continue Prednisolone 5 mgm bd.

DISCUSSION

The patients described were extremely ill, with intense bronchospasm and severe ventilatory failure. It is not likely that either would have survived had intensive resuscitative measures not been employed. Clinical severity had not been appreciated at the outset of Cases 1a and 1b, and there was considerable delay before blood gas analysis was requested. Case 2a was studied soon after the onset of severe symptoms; in Case 2c, however, the initial Po_2 of 60 mm Hg and Pco_2 45 mm Hg engendered a sense of false security and subsequent

deterioration was unexpected and rapid. An orderly plan of therapy intended to allow subsequent appraisal of the treatments employed is exceedingly difficult to design and implement in acute life threatening situations. Several therapeutic agents may be used concurrently, thereby rendering individual assessment difficult or impossible. This reservation undoubtedly applies to the present studies and the following comments on treatment are therefore somewhat tentative - further experience and more precise information is required before a rational risk-free approach to the management of such cases can be outlined.

Initial treatment with oxygen was followed by a rise in Pco_2 in Cases 1b and 2a. The coincidental administration of sodium bicarbonate may have been partially responsible for the rise in Pco_2 following an increase in the inspired oxygen concentration in Case 1a. Even so, this experience suggests that the indiscriminate use of oxygen is unsafe.

Sodium bicarbonate was infused on seven occasions. Although this undoubtedly helped maintain a pH > 7.25, the striking relief of bronchospasm and reversal of the moribund state noted in adults after correction of acidosis with sodium bicarbonate (Mithoefer et al., 1965, 1968) was not observed in these children. The experience of these authors included the successful resuscitation of a 12 year old child with severe ventilatory failure due to asthma, in whom arterial pH was 6.66. Pco_2 fell from a level above 250 mm Hg to 82 mm Hg and pH rose to 7.27 following the administration, in divided doses, of 110 mEq sodium bicarbonate. Manual ventilation using a rubber bag at an initial pressure of 70 mm Hg was undertaken simultaneously. Assuming that this patient was of average weight for age, the amount of sodium bicarbonate infused was approximately 3 mEq/Kg B.Wt., which is half the maximum

dose employed here (5-6 mEq/Kg, Case 2c) and which resulted in a change in pH from 7.03 to 7.23 (Table 25) with little change in Pco_2. The striking decrease in airway resistance appreciated by the physician compressing the rubber bag in Mithoefer's (1968) patient, was not noted in either patient 1 or 2 before the use of ether. The risk of this or higher doses is uncertain, but may be appreciable(Finberg, 1967; Posner and Plum, 1967). Serum electrolyte concentrations before and after the administration of sodium bicarbonate are shown in Table 26. Hypernatraemia, with serum sodium concentrations greater than 150 mEq/litre was produced in Cases 1a and 2c. Both children recovered without obvious ill effects, however, and Case 2c remains well above average in school performance. It seems likely that the advantages of this form of therapy outweighs its theoretical drawbacks.

The response to adrenaline following sodium bicarbonate infusions was not tested, as the patients were either extremely drowsy or unconscious with marked tachycardia and Pco_2 levels above 80 mm Hg. This aspect of treatment is fully discussed by Mithoefer et al., (1965, 1968).

During recovery hypochloraemia and hypokalaemia were observed in Case 1a. Renal loss of chloride is part of the compensatory mechanism for respiratory acidosis (Polak et al., 1961) and depletion of body store of chloride may occur (Robin, 1963). Metabolic alkalosis associated with hypochloraemia may therefore occur when carbon dioxide tension is lowered with recovery from acute respiratory insufficiency (Schwartz et al., 1961). Potassium depletion may also contribute to the development of metabolic alkalosis in this situation (Refsum, 1962).

Manual ventilation was employed as a suitable mechanical ventilator was not available. High pressures (not measured) were required to inflate the lungs on each occasion. After three hours of manual

ventilation the Pco_2 in Case 2a remained dangerously high, and for that reason ether anaesthesia was used, as described by Tausig et al., 1952. Deep ether anaesthesia resulted in immediate release of bronchospasm and manual ventilation was accomplished with ease. Bronchospasm of varying degree invariably recurred when ether was stopped. Thereafter, recovery was assisted by further infusions of sodium bicarbonate (Case 1a) and intravenous aminophylline (Case 2c). Dehydration had been corrected by this stage in each case, and it is likely that corticosteroid drugs had become fully effective (Vaughan, 1965).

During assisted ventilation and ether anaesthesia, hypotension (Cases 1a, 1b and 2c), hypothermia (Case 2c), ECG abnormalities (Case 2c), and lactic acidosis (Case 2c) - see Section VI - were observed. The rapid fall in Pco_2 and the circulatory effects of positive pressure ventilation may partially explain the occurrence of hypotension and possibly lactic acidosis. The ECG changes during ether anaesthesia (Figure 18) have been reported previously (Lennox, 1922; Miller, 1925; Stazhadze, 1967). The danger of producing hyperkalaemia by hyperventilation (Hickam et al., 1956; Scribner et al., 1951), and possibly cardiac arrest was fully recognised, but following the use of ether even gentle manual ventilation produced a marked reduction in Pco_2. Serum potassium concentration was not measured at this stage in any of these patients.

The use of ether is not therefore without considerable hazard and has been abandoned in certain centres specially equipped to deal with the ventilatory problems these patients present. With adequate prior preparation and a coordinated team approach, it may have been possible to institute the regime of treatment suggested by Downes et al., 1965, and to have obviated the need for ether anaesthesia. Williams and

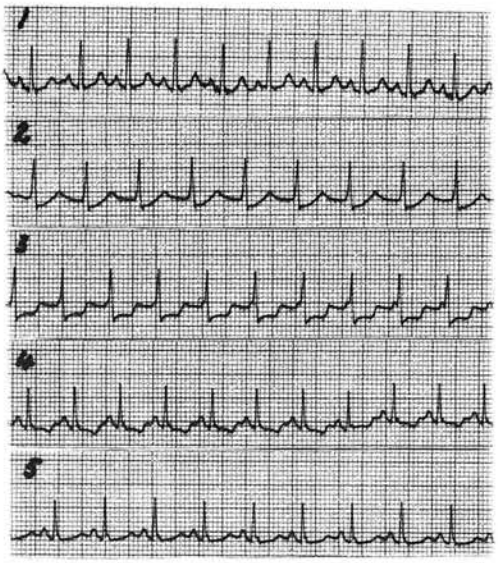

Figure 18 ECG changes in relation to ether anaesthesia (Case 2c)

Time

11.05 1. Before the administration of Ether - a 1 mm depression of the ST interval followed the intravenous injection of 60 mgm scoline.

11.25 2. Five minutes after the administration of Ether - Rate 150/minute Nodal rhythm with 2 mm sag in ST interval.

11.26 3. Six minutes after the administration of Ether - persistent depression of ST interval; T wave inversion; sinus rhythm re-established.

11.32 4. On reduced concentration of Ether. Two minutes after reduction ECG has almost returned to normal apart from a low but upright T wave and 1 mm ST sag.

11.50 5. Light ether anaesthesia. ECG remains unchanged.

Crooke, 1968, however suggest that ether is the ideal volatile anaesthetic agent in this situation, and continue to recommend its use followed by bronchial lavage in severe status asthmaticus in adults.

SUMMARY

The management of four episodes of severe respiratory failure occurring in two patients is described. Measurements of blood gas tensions and pH, by repeated arterial puncture were used to guide progress, and help rationalise decisions on treatment. Despite the successful outcome in these patients, the regime adopted was not without hazards. The importance of advance preparation in the form of adequate facilities to assist ventilation, and the coordination of medical, anaesthetic and laboratory skills is emphasised.

S E C T I O N I V

CYSTIC FIBROSIS OF THE PANCREAS

BLOOD-GAS TENSIONS AND pH IN CYSTIC FIBROSIS

INTRODUCTION

The symptoms of cystic fibrosis are related to a generalised dysfunction of exocrine glands, resulting in chronic pulmonary disease, pancreatic deficiency, and abnormally high sweat electrolytes in most patients. The pulmonary involvement in cystic fibrosis may vary considerably, and to a large extent the variations in the manifestations and course of the disease are determined by the degree to which the lungs are affected. Studies of pulmonary function mainly in children old enough to cooperate actively show that obstructive airway disease is the main functional abnormality, (West et al., 1954; Cook et al., 1959; Doershuk et al., 1965; Beier et al., 1966; Mearns, 1968; Mellins et al., 1968; Phelan et al., 1969; Featherby et al., 1969; Godfrey and Mearns, 1971). Many of these studies show the correlation between clinical state and the results of the various tests of airway obstruction.

Until recently there had been few published reports on blood gas tensions and pH in cystic fibrosis. The occurrence of hypoxaemia, even in mildly affected patients is now well recognised, (Goldring et al., 1964; Beier et al., 1966; Caplan and Gross, 1968; Featherby et al., 1969). In contrast to the low Po_2 the partial pressure of CO_2 in arterial blood is usually normal or slightly decreased, (Beier et al., 1966; Wise and Beaudry, 1968) though a sustained rise may occur in the late stages of the disease (Wise and Beaudry, 1968). Promadhat (1966) measured the Pco_2 in 67 infants with cystic fibrosis using the rebreathing technique of Collier (1956) and found that hypercapnia was often present during exacerbations, and sometimes took weeks or months to subside.

In the present study arterial or arterialised capillary blood gas tensions and pH were measured in 25 infants and young children with

cystic fibrosis at various stages in their illnesses. Conventional tests of pulmonary function not involving sampling of blood were not readily applicable as 19 of the children were under 6 years of age. The results obtained were related to assessments of clinical status made in each patient at the time of sampling. The changes occurring in blood gas tensions and pH during oxygen therapy were also investigated.

PATIENTS

Twenty-five patients, 14 boys and 11 girls, with cystic fibrosis, age 4 weeks to 12 years, were selected for study. They constituted all the available patients who were being treated between 1965 and 1968 at the Royal Hospital for Sick Children in Edinburgh. The diagnosis was established by clinical criteria, raised sweat electrolytes, and the absence of tryptic activity in duodenal juice. Clinical details of these patients at the time of admission to the study are given in Table 27. The clinical grading system adopted (Table 28) was applied before each study in all patients, many of whom were studied in different clinical states. This system was simple, and could be applied without awaiting the results of bacteriological investigations, or X-raying the chest at each assessment. The number of studies in each patient at the various clinical grades is shown in Table 29. Most were carried out during a period of assessment or treatment in hospital. Nearly half the total number of measurements were made in only four patients, however, Cases 11, 12, 16 and 19, all of whom were less than six months old when first investigated. The clinical management of the majority of cases was standardised by one physician who decided about hospital admission, discharge, or further out-patient care on the basis of his clinical judgement.

RESULTS

Of the 25 original patients 18 survived and seven died (Cases 11, 12, 13, 16, 23, 24 and 25) during the period of the study (1965-1968). Four of the patients who died had presented with respiratory problems in the early weeks of life and survived less than one year, (Cases 11, 12, 13 and 16). The others (Cases 23, 24 and 25) were only studied during their terminal illnesses. The clinical diagnoses were confirmed in the six patients in whom autopsy was performed.

Children in Grade I (Table 27) remained well and were managed as out-patients. Of the patients in Grade II at the outset two were managed as out-patients (Cases 8 and 9) and three (Cases 10, 11 and 12) alternated between Grades II and IV and spent many months in hospital. Grade III patients who survived continued in that grade or varied between Grade III and Grade II. All Grade IV patients (Cases 23-25) died within days of initial investigations. No patient graded IV at any time during the course of his illness survived more than four months thereafter. The clinical course of one patient (Case 12) who varied between Grades II and IV, and died at the age of 6 months, is summarised in Table 30.

The mean values, standard deviation (S.D.) and ranges of acid-base variables in arterial, or arterialised capillary blood in the different clinical grades, breathing air, are shown in Table 31. There is a progressive fall in Po_2 with significant difference in Po_2 between Grades I and II ($P < 0.001$) and Grades II and III ($P < 0.001$). There were too few observations in Grade IV to allow comparison with Grade III. The mean Pco_2 is within normal limits in Grades I and II but the respective levels are significantly different ($0.01 > P > 0.002$). In Grade III the mean Pco_2 is slightly greater than normal and differs

significantly from the mean Pco_2 in Grade IV ($P < 0.001$) in which Pco_2 rises precipitously. Mean pH is within normal limits in Grades I-III. The mean pH of 7.33 in Grade IV is significantly different from the pH in Grade III ($P < 0.001$). There is a progressive fall in arterial oxygen saturation and increase in alveolar arterial oxygen tension differences from Grades I-IV. Mean base excess rises throughout the various grades, a steep rise occurring in Grade IV. The mean haemoglobin concentration is similar in all four clinical grades. Composite data for the entire group (Grades I-IV) based on initial measurements in patients in each group are compared with the results of other series in Table 32.

In all patients with definite respiratory symptoms and signs (Grades II, III and IV) respiratory and pulse rates were significantly related to Po_2 and Pco_2 (Figs. 19-22). Restlessness was seldom seen, even with severe hypoxaemia; unequivocal cyanosis was only observed in patients in Grade IV (Mean So_2=81.8%).

The time course of changes in Pco_2 in individual cases is shown for six patients during seven exacerbations of infection (terminal in Cases 11, 12 and 13) in Figure 23. Case 16 died within the following six months; Cases 10 and 19 survived the period of the study but ultimately died of respiratory complications, 2 and 4 years later respectively. Patients in Grade IV (Cases 22-25) had Pco_2 levels >80 mm Hg whilst breathing oxygen during their terminal illnesses. Three other patients developed carbon dioxide retention during episodes of infection (Case 8, Pco_2 46 mm Hg; Case 20, Pco_2 54 mm Hg, Case 21, Pco_2 53 mm Hg) - all are alive four years later.

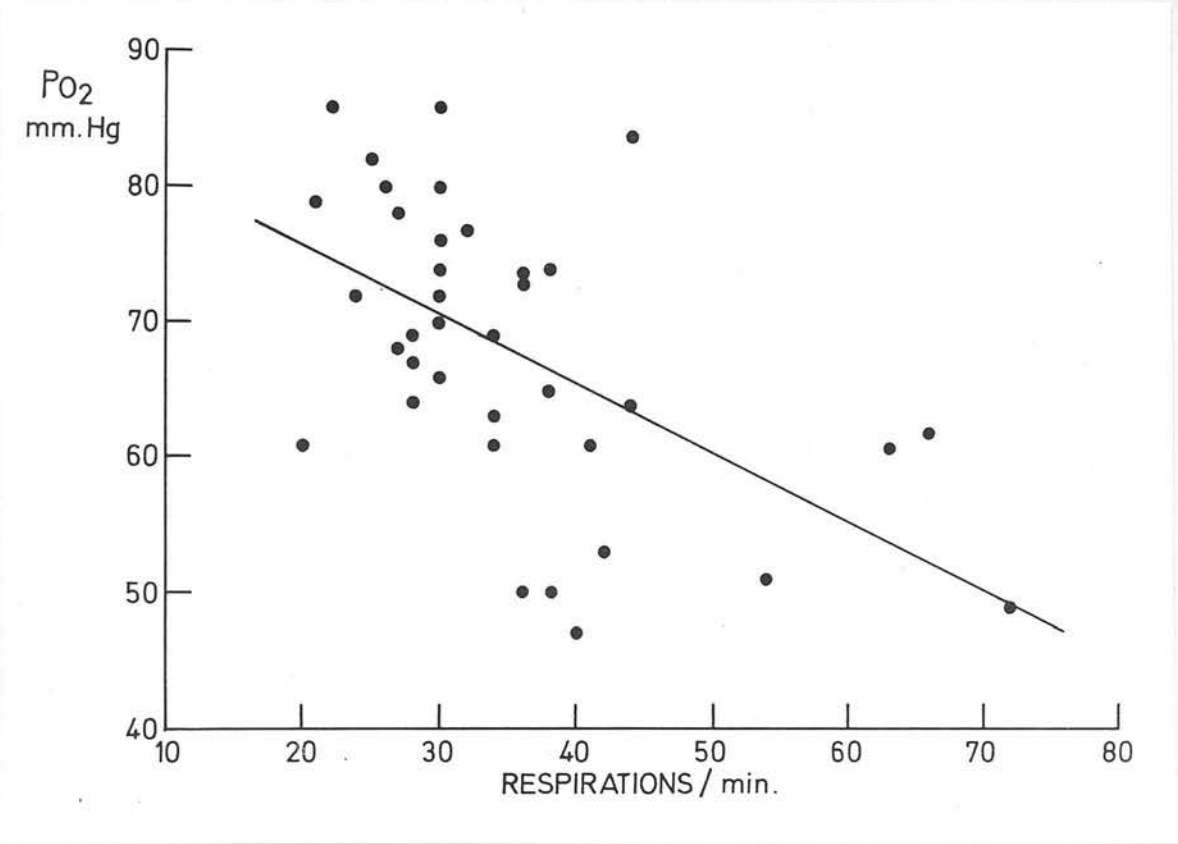

Figure 19

Relation between respiratory rate and Po_2, when breathing air (Grades II, III and IV).

$$Po_2 \text{ mm Hg} = -0.49 \text{ respiratory rate} + 85$$

$$r = -0.537 \; ; \; P < 0.001$$

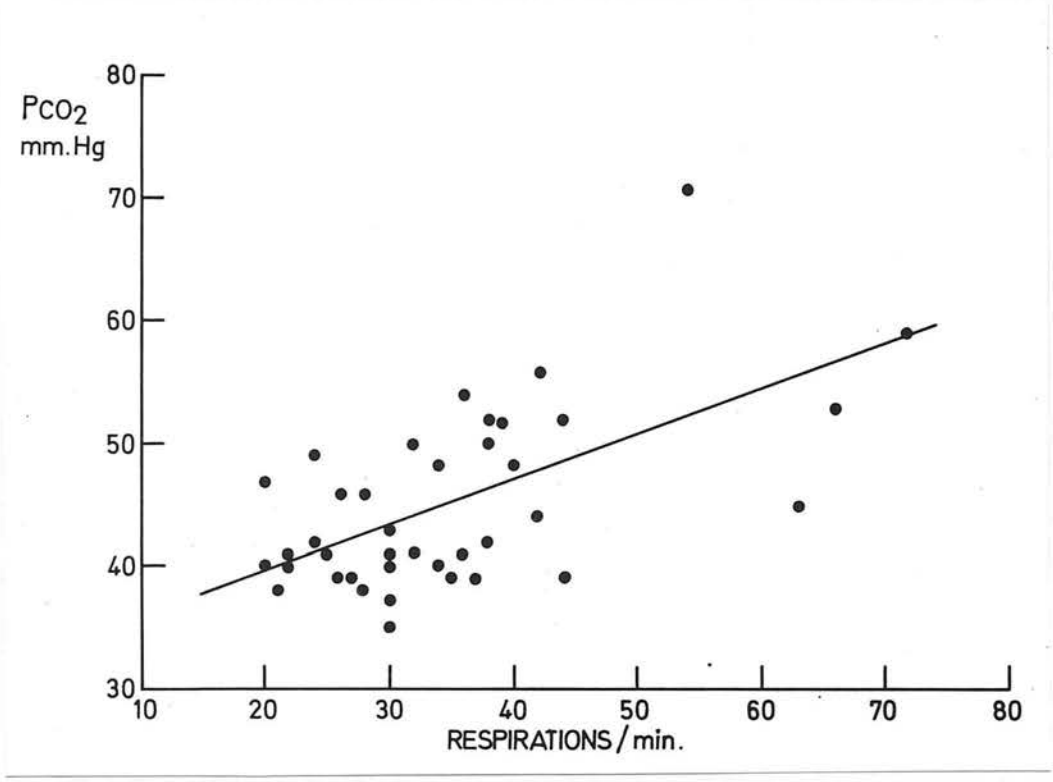

Figure 20

Relation between respiratory rate and Pco_2 when breathing air (Grades II, III and IV).

$$Pco_2 \text{ mm Hg} = 0.35 \text{ respiratory rate} + 33$$

$$r = 0.586 \; ; \; P < 0.001$$

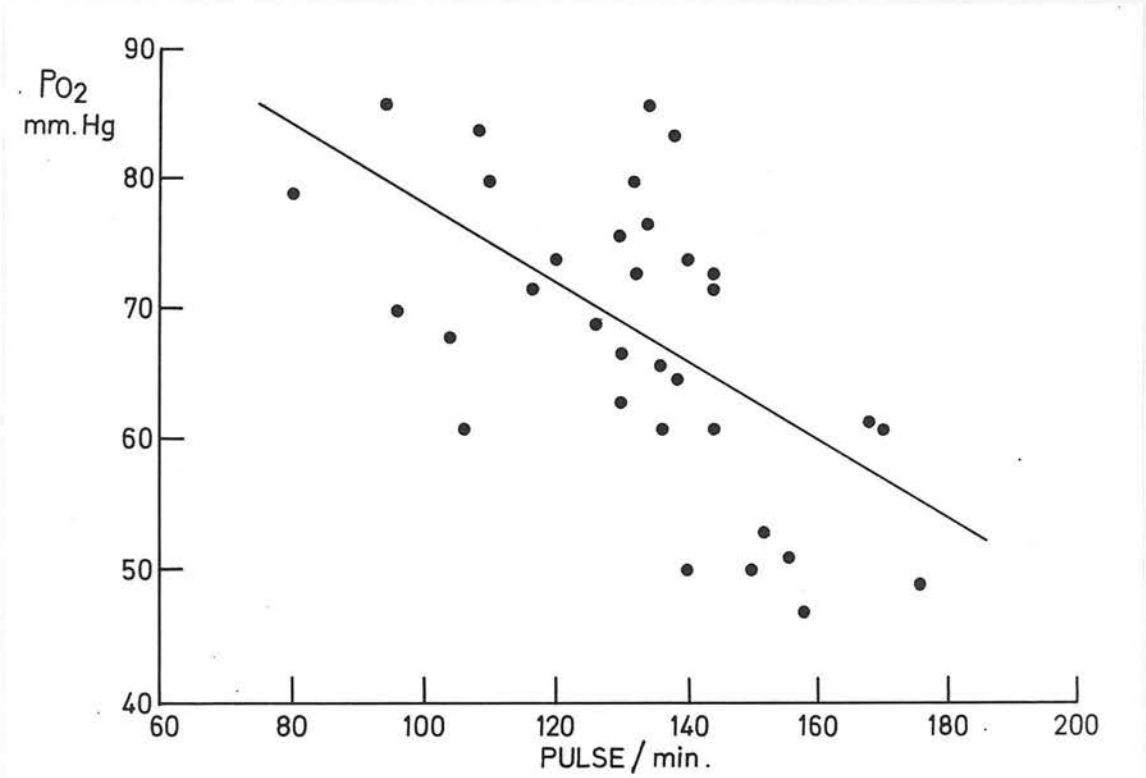

Figure 21

Relation between pulse rate and Po_2, when breathing air (Grades II, III and IV).

$$Po_2 \text{ mm Hg} = -0.30 \text{ Pulse rate} + 109$$

$$r = -0.599 \; ; \; P < 0.001$$

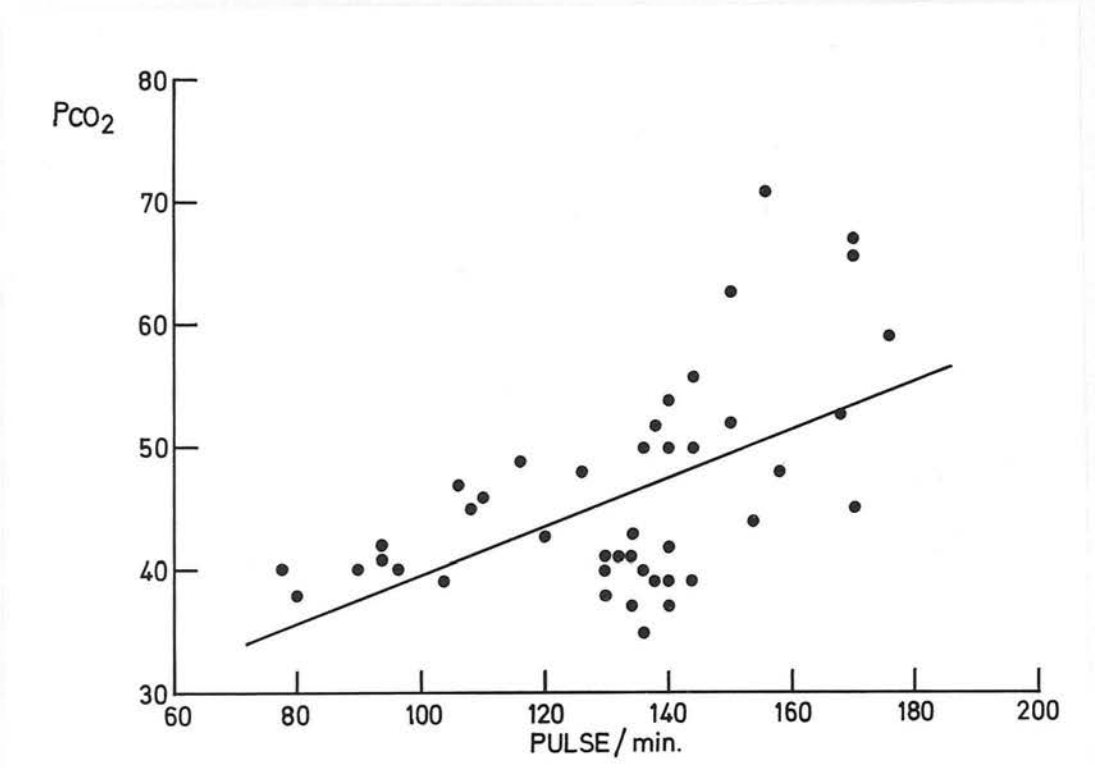

Figure 22

Relation between pulse rate and Pco_2, when breathing air.

Pco_2 mm Hg = 0.20 pulse rate + 20

$r = 0.559$; $P < 0.001$

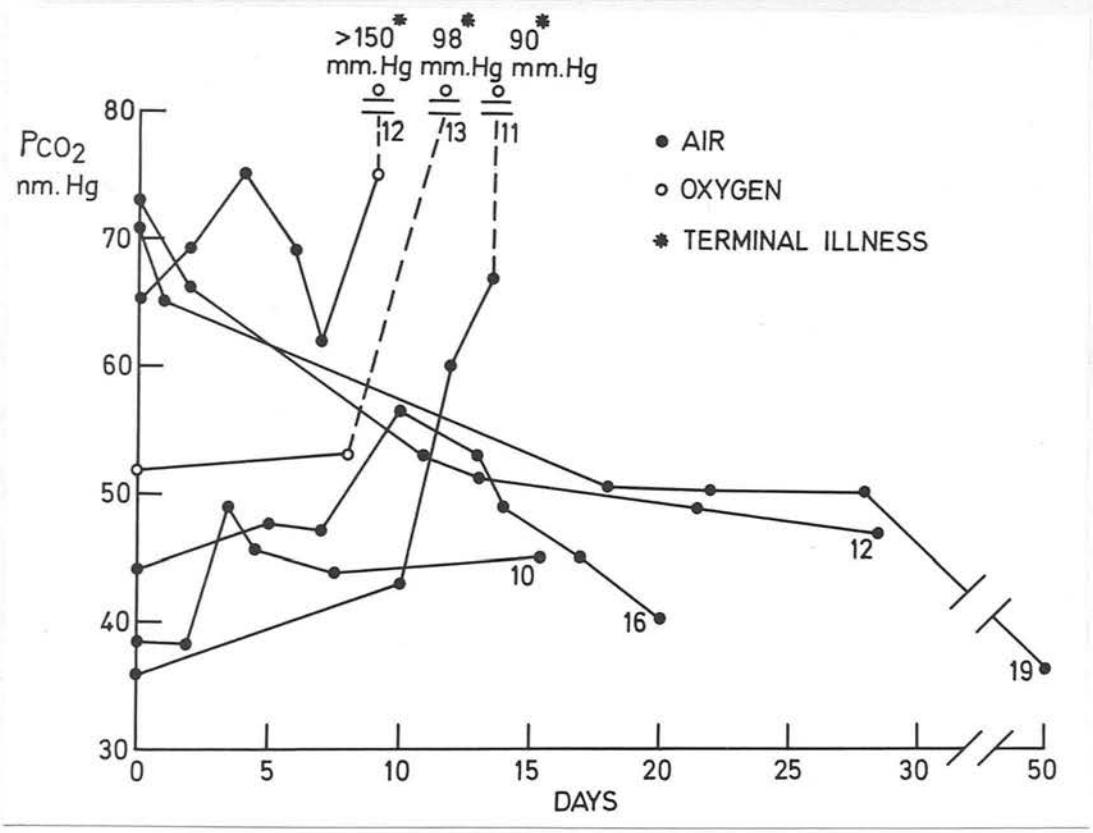

Figure 23

Time course of changes in Pco_2 during exacerbations of infections in seven patients. Uncontrolled hypercapnia and circulatory failure supervened in Cases 11, 12 and 13.

EFFECTS OF BREATHING OXYGEN

Eight patients were studied on nineteen occasions before and during the administration of 40 or 100 per cent oxygen for some thirty minutes (Table 33). Arterial Po_2 rose to within normal limits or above on each of the six occasions when measurements in air and oxygen were made. No change occurred in Pco_2 when initial values in air were within the normal range. When the Pco_2 exceeded 45 mm Hg in air (Figure 24) a rise in Pco_2 accompanied by a fall in pH occurred in two patients (Cases 12 and 16). The most striking change occurred in Case 12 (Grade IV) in whom the breathing of 90-100 per cent oxygen resulted in an increase in Pco_2 from 63 to 84 mm Hg and a fall in pH from 7.39 to 7.29. Pco_2 returned to its original value after several hours following the reduction of the inspired oxygen concentration to between 25 and 30 per cent. No other patient with carbon dioxide retention in air had been given 100 per cent oxygen to breathe. The reduction in Pco_2 and rise in pH seen in three patients (Cases 13, 15 and 20) was probably related to crying or hyperventilation when the second blood sample was taken.

The alveolar-arterial oxygen tension difference was calculated for patients breathing air, and 40 per cent oxygen. Resting values were usually greater than normal and rose markedly on each occasion during oxygen therapy.

DISCUSSION

Many studies have shown the correlation between clinical state and tests of lung mechanics in cystic fibrosis. This subject has recently been fully discussed (International Cystic Fibrosis Conference 1969).

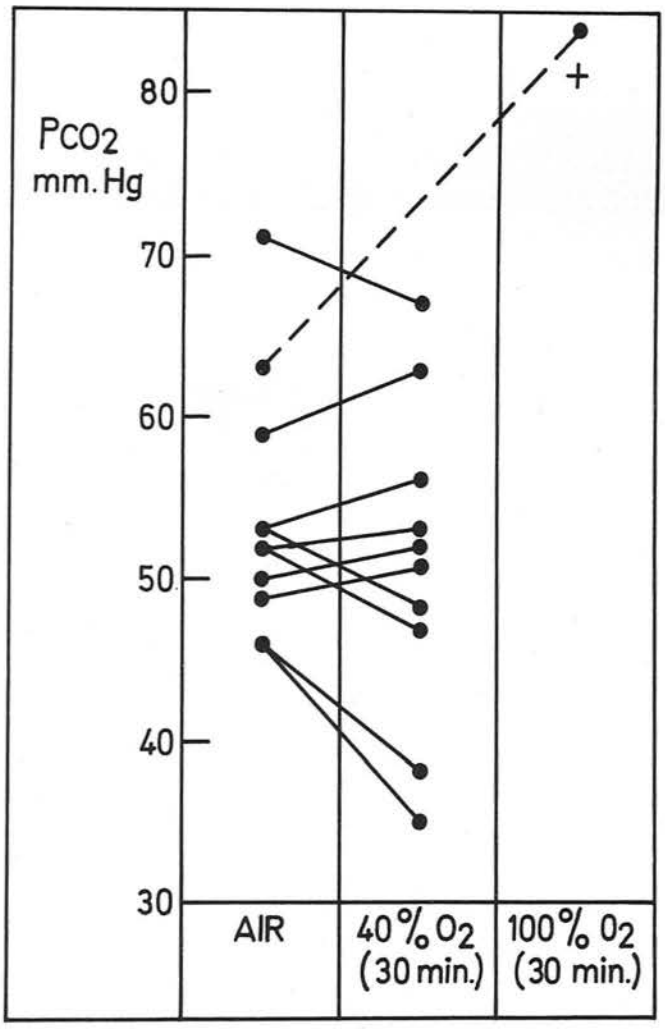

Figure 24

Effect of breathing oxygen on Pco_2 during eleven studies on eight patients.

+ No study in 40 per cent oxygen (Case 12)

Correlation with Clinical Features

The clinical grading system (Table 28) was applied to patients with varying degrees of pulmonary involvement. It was different from most other clinical scoring systems, notably that of Schwachman and Kulizycki (1958) in that only variables relating to pulmonary function were considered. Essentially it divided patients into two main groups depending on the presence or absence of overt signs of infection in the lungs. Infection associated with pyrexia and systemic illness was seen so uncommonly that patients showing these signs were considered separately. The results emphasise the importance of secondary infection in determining pulmonary function status in these patients. Severe infection with systemic upset carried grave prognostic implications.

The good correlation between respiratory and pulse rates and measured values of Po_2 and Pco_2 (Figs.19-22) contrasts with the situation in acute respiratory failure in pneumonia and asthma where clinical signs of hypoxia and carbon dioxide retention are often misleading. This confirms the findings of Caplan and Gross (1968); Matthews et al. (1969); and Featherby et al., (1969) who demonstrated a good relationship between clinical scores based on a modification of the Schwachman and Kulizycki (1958) system, and arterial oxygen tension. No clinical method of scoring has yet been reported, however, which is of practical use in predicting blood gas tensions in the individual patient.

Hypoxaemia and its Mechanisms

A low arterial Po_2 in these cases confirms previous reports. In a series of 21 patients with cystic fibrosis, ages 6 to 22 years, Goldring et al. (1964) report an arterial oxygen saturation ranging from 31-100 per cent, with the saturation below 90 per cent in eight

patients. Arterial oxygen tension (Po_2) varied between 42 and 85 mm Hg in 15 patients studied by Beier et al. (1966). In 64 observations in 49 patients, ages 6 to 27 years, Featherby et al. (1969) found a mean Po_2 of 77.7 mm Hg which compares with the findings for Grade II (mean Po_2 74.9 mm Hg). The subjects studied by Featherby et al. (1969) were probably well enough to have been followed up as out-patients though no mention is made of the relative number of in-patient and out-patient studies.

A low arterial Po_2 could result from alveolar hypoventilation as shown by a raised Pco_2. Alternatively hypoxaemia could result from an imbalance of ventilation and perfusion in the lungs with limitation of available area of blood gas exchange, a diffusion barrier to the passage of oxygen, or increased venous admixture due to right-to-left intrapulmonary shunts. The significant relationship between Po_2 and Pco_2 (Figure 25) shows that hypoventilation is of importance in these cases, and is a reflection of the number of severely affected children investigated. The raised alveolar-arterial oxygen tension differences which increase markedly during the correction of hypoxaemia with moderate oxygen enrichment of the inspired air strongly suggest a ventilation/perfusion abnormality. This has been shown more precisely by the increased alveolar-arterial nitrogen gradients which occur in this condition (Baudry et al., 1960; Waring, 1965; Waring et al., 1968). Tests of alveolar membrane diffusion based on the ability to transfer carbon monoxide from the alveoli to blood show a reduction in "diffusing capacity" in later stages of the disease (Godfrey and Mearns, 1971) which may further contribute to hypoxaemia. These findings may, however, be merely a reflection of ventilation/perfusion imbalance (West, 1965). Right-to-left intrapulmonary shunts varying from 11 to 37 per cent of

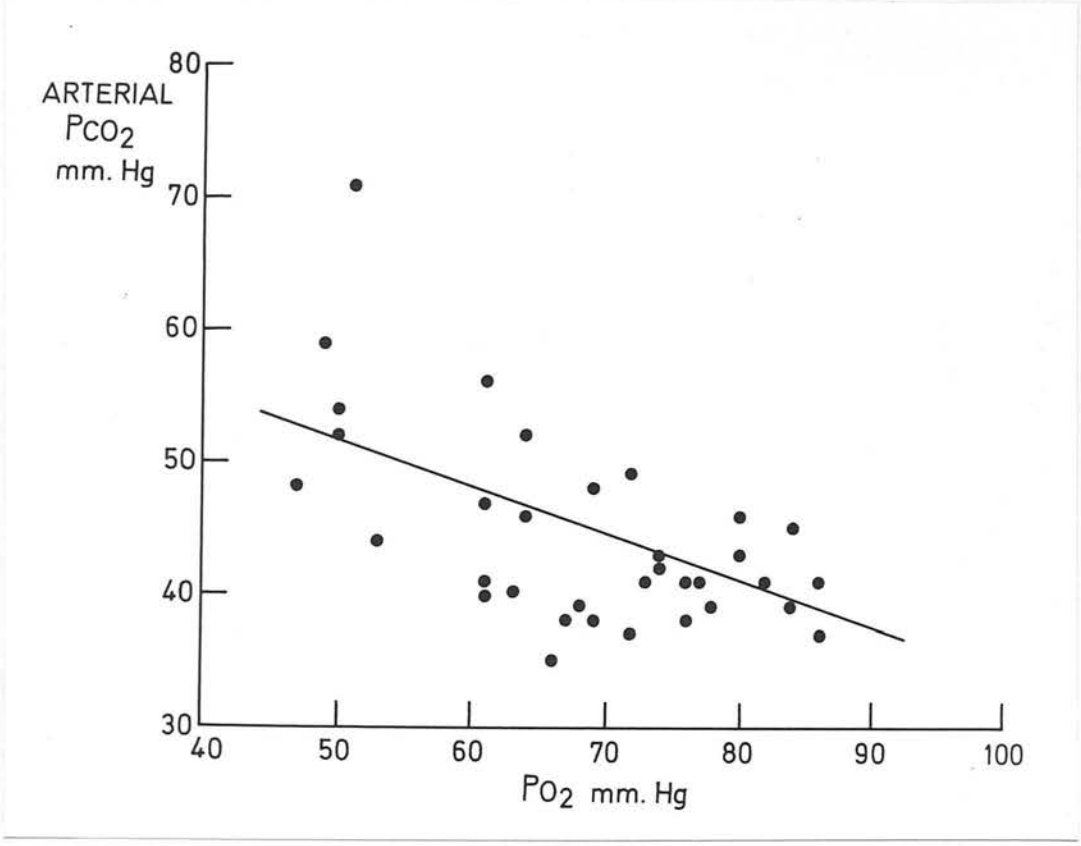

Figure 25

Relation between arterial Po_2 and Pco_2 when breathing air (Grades II, III and IV).

$$Pco_2 \text{ mm Hg} = -0.35\ Po_2 \text{ mm Hg} + 68.8$$

$$r = -0.662\ ;\ P < 0.001$$

cardiac output have been reported by Moss et al. (1965) during cardiac catheterisation studies in eight patients. It seems likely therefore that all of these mechanisms contribute to the hypoxaemia in cystic fibrosis which may ultimately lead to pulmonary hypertension, cor pulmonale and death (Goldring et al., 1964).

The similarity in haemoglobin concentration in the various grades was an unexpected finding as iron absorption is known to be normal or even increased in severely affected patients with cystic fibrosis (Tonz et al., 1965). Caplan and Gross (1965) demonstrated a significant inverse relationship between Po_2 and haemoglobin in 87 patients with cystic fibrosis. Decreased utilisation of iron due to persistent secondary infection may explain the findings in the present series.

Hypercapnia and Acid/Base Balance

Hypercapnia occurred during exacerbations of infection and was an invariable terminal occurrence. Only one patient in Grade II had a Pco_2 greater than 50 mm Hg (Case 21, aged 4 months, Pco_2 53 mm Hg). This experience confirms the observations of Promhadhat (1966) and Wise (1968). Beier (1966) explained the low Pco_2 in many of his patients on the basis of hyperventilation that accompanied the trauma of arterial puncture. This factor was not likely to have significantly affected results here as the lowest Pco_2 even in Grade I was 34 mm Hg.

A significant reduction in pH was found only in the most severely affected patients in Grades III and IV. The lowest pH recorded in any patient breathing air (Case 12, pH 7.26, Pco_2 73 mm Hg) was higher than that found in patients with pneumonia or asthma with a comparable degree of carbon dioxide retention. Figure 26 shows the significant relationship between Pco_2 and base excess. Negative values of base excess associated with a low Pco_2 were uncommon. The high positive

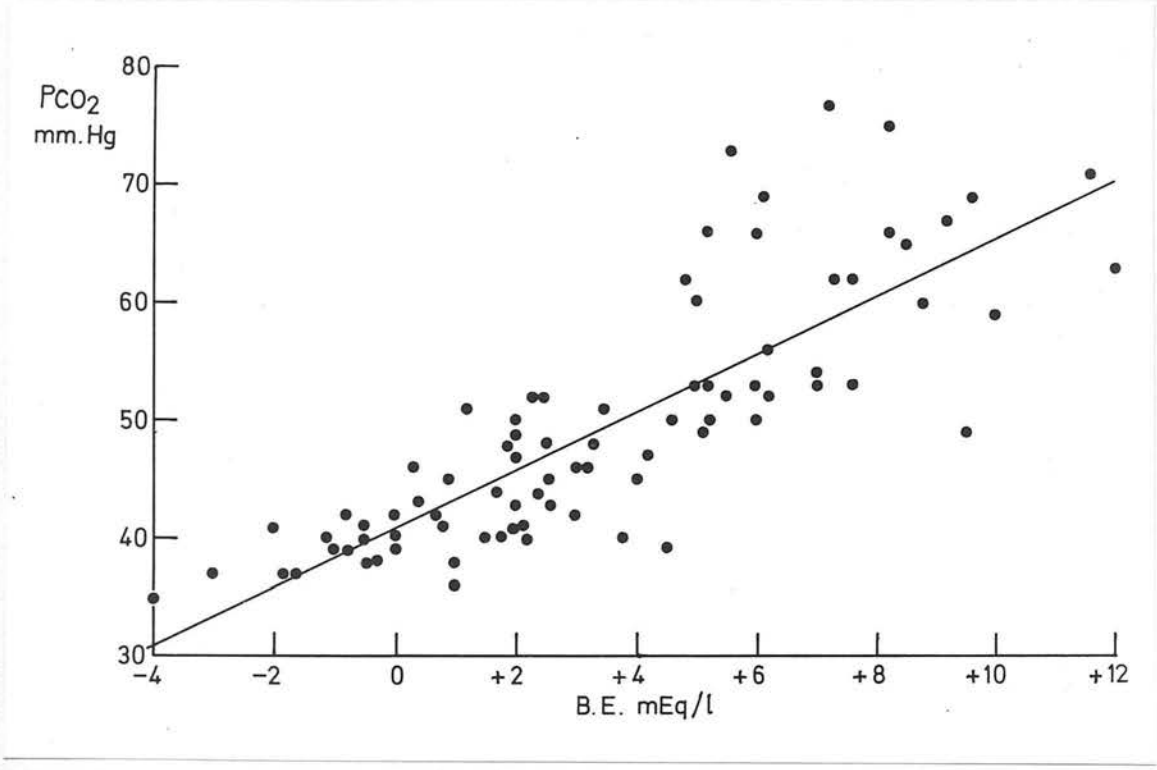

Figure 26

Relation between Pco_2 and Base Excess, breathing air (Grades II, III and IV).

$$Pco_2 \text{ mm Hg} = 2.47 \text{ B.E. mEq/l} + 40.9$$

$$r = 0.823 \; ; \; P < 0.001$$

values of base excess in patients with carbon dioxide retention suggest that renal reabsorption of bicarbonate occurs in these children, and is an important defence against respiratory acidosis, as it is in the adult (Refsum, 1964). The significant difference in the relationship of Pco_2 to base excess in cystic fibrosis compared to acute pneumonia ($0.002 > P > 0.001$) reflects the lag in renal reabsorption of bicarbonate during acute respiratory failure in the latter condition.

Observations on blood lactate and pyruvate concentrations in six of these patients (Cases 1, 2, 4, 7, 11, 17) are reported in Section VI. These suggest that significant lactic acidosis only occurs during acute exacerbations of infection.

Effects of Oxygen Therapy

Hypoxaemia was invariably corrected following the administration of 40 per cent oxygen (Table 33), an inspired oxygen concentration which should be attained in most conventional tents (Simpson and Russell, 1967). An increase in Pco_2 during oxygen therapy is a well recognised danger in treating respiratory failure in the adult (Donald, 1949; Comroe et al., 1950; Westlake et al., 1955). It may also be a hazard in the treatment of severe acute asthma in children (Simpson et al., 1968). The results suggest that there is little danger of producing a further rise in Pco_2 when initial Pco_2 is normal. The danger of injudicious oxygen therapy when the Pco_2 is elevated has been recognised previously (Bruck, 1957; Goldring et al., 1964). Bruck (1957) reported severe ventilatory failure with loss of consciousness following the administration of a high concentration of oxygen in two children with cystic fibrosis; resuscitation with intermittent positive respiration was necessary in each case. In the series reported by Goldring et al. (1964), breathing

40 per cent oxygen produced a further rise in Pco_2 in five patients in whom the resting Pco_2 exceeded 50 mm Hg. An increase in Pco_2 from 60 to 78 mm Hg occurred in one patient; corresponding pH values were not given. Efficient means of providing controlled oxygen concentrations to lessen the hazard of carbon dioxide narcosis have been suggested by Campbell (1960), Flenley et al. (1963) and Campbell and Gebbie (1966) for the treatment of exacerbations of infection in adults with chronic bronchitis. Face masks and head tents are poorly tolerated by young children, however, and an effective means of providing controlled oxygen concentrations acceptable to young children has not yet been devised.

Prognostic Value of the Acidosis

Uncontrolled carbon dioxide retention with levels varying from 58 to 150 mm Hg whilst breathing oxygen were seen during the terminal illnesses of the seven patients who died in this series. pH was maintained above 7.25 in all but one patient (Case 12, Table 30). An increase in Pco_2 occurred in a further five patients during exacerbations of infection. Of these, only three are alive four years later (Cases 8, 20 and 21). It thus seems from this limited experience that elevation of Pco_2, particularly if prolonged, carries grave prognostic implications even when pH is maintained above 7.25. Although judicious oxygen therapy is of importance when carbon dioxide retention occurs, an active programme of bronchial care is essential from an early stage in the disease. The detection and correction of hypoxaemia may be of great value in preventing and treating the cor pulmonale which eventually occurs in most patients.

SUMMARY

Arterial or arterialised capillary blood gas tension and pH were determined in 25 patients with cystic fibrosis. A clinical grading system based on an assessment of respiratory variables and the presence or absence of pulmonary infection was adopted, and proved to be of value in predicting hypoxaemia. Hypoxaemia occurred at an early stage in the disease and was often severe during episodes of infection. Pco_2 was usually normal, but hypercapnia occurred occasionally during exacerbations of infection and was invariable in the later stages of the disease. The hazards of injudicious oxygen therapy are also confirmed.

S E C T I O N V

USE OF ALKALI IN ASPHYXIA NEONATORUM

ALKALI THERAPY IN ASPHYXIATED NEWBORN INFANTS

The effectiveness of infusions of alkali and glucose in facilitating recovery and preventing brain damage has been demonstrated in asphyxiated newborn animals, (Dawes et al., 1963, 1964; Adamson et al., 1963, 1964). It was argued that since ventilation alone may cause a gradual decline in arterial Pco_2 and hydrogen ion concentration, the rapid correction of pH by injection of alkali and glucose during resuscitation might be an additional help by reducing pulmonary vascular resistance and by partial restoration of the normal cellular environment. Largely as a result of these studies paediatricians now often undertake the rapid correction of acidosis in the delivery room by infusing alkali into an umbilical vessel, with or without acid-base monitoring. At the present time, however, no studies have been reported on the results of this form of treatment. Observations are presented here on the use of sodium bicarbonate as an adjunct to assisted ventilation in the resuscitation of asphyxiated newborn infants. These were made during the management of 'high risk' newborn infants in the delivery area of the Newborn Nursery at the Moffat Hospital, University of California, San Francisco, as part of a larger study on physiological adaptations in the immediate newborn period.

PATIENTS

The investigation comprised a total of 23 newly born infants (16 singletons, two pairs of twins, one set of triplets) who were studied during the first hour of life. They were selected from 26 infants studied in the immediate newborn period for one or more of the following reasons - antepartum haemorrhage, prolonged labour, foetal distress, traumatic delivery, birth weight under 1500 G, asphyxia neonatorum,

cardiopulmonary distress, or a history of a previous infant with severe respiratory distress. Three groups of infants were defined -

Group 1

Sodium bicarbonate was not used in the treatment of the six infants in this group. They are not ideal controls, however, as only two were asphyxiated at birth. It was not considered justifiable to withhold treatment from severely asphyxiated infants. Four were intubated and ventilated manually for a variable period of time.

Group II

Infants in this group were not unduly asphyxiated at birth (Apgar score ≥ 5). Sodium bicarbonate was infused on the basis of persistent metabolic acidosis, indicated by the results of blood gas analysis.

Group III

These infants were asphyxiated at birth (Apgar score < 4) and received infusions of sodium bicarbonate as an adjunct to positive pressure ventilation. Prior blood samples were taken for gas analysis but the results were not always known when alkali infusions were started.

Hypovolaemia was considered to be a major problem in the three patients excluded from the study. Albumen was infused in these cases to correct hypotension; sodium bicarbonate was not used in their immediate management.

PROCEDURE

The delivery of these infants had been anticipated and preparations had been made for their arrival. Members of the paediatric, anaesthetic and nursing staff conducted the resuscitative and investigative procedures which were undertaken.

In infants obviously asphyxiated at birth the cord was clamped almost immediately to allow resuscitative measures to proceed; in most others cord clamping was delayed until the first respiratory efforts had been made. Each infant was blotted dry with a towel at birth and thereafter

resuscitation was conducted under a radiant heat source. Needle ECG electrodes were inserted within the first minute. Rectal temperature was monitored continuously and maintained at or near 36.5°C. The upper airway was cleared in each case and 17 infants were intubated and ventilated with intermittent positive pressure (monitored with a pressure gauge) using oxygen or oxygen enriched air. Initial ventilation included two or three prolonged inspiratory phases of three to four seconds each with a sustained pressure of 30 to 40 cm of water. An umbilical arterial catheter was inserted as quickly as possible and used to obtain blood samples, to infuse sodium bicarbonate and to monitor mean lower aortic blood pressure. Acidosis was corrected with 0.89 Molar Sodium bicarbonate in a dose range of 1.5-4 mEq/Kg body weight given over a period of one to three minutes. A larger dose, 6 mEq/Kg, was used in the treatment of one infant with severe intra-uterine asphyxia (Case 20). The mean age at the start of sodium bicarbonate injections was 14 minutes. Blood samples for determination of gas tensions, pH, haemoglobin and haematocrit were obtained before and soon after the infusion of alkali and thereafter as determined by clinical progress and the results of these tests. The inspired oxygen concentration was regulated throughout this time so as to give no more than necessary for adequate saturation of arterial blood. Frequent sampling of arterial Po_2 and appropriate adjustment of inspired oxygen concentration was usually required following recovery from asphyxia before a stable state was achieved.

RESULTS

Clinical details of the 23 infants are given in Table 34. Nineteen survived. Eight patients (Cases 1, 2, 7, 13-17), six of whom weighed

less than 1500 G at birth developed I.R.D.S. and three died (Cases 7, 16 and 17). The fourth death was that of the infant with severe intrauterine asphyxia (Case 20) and an Apgar score of zero at birth. Attempts to resuscitate this baby using intermittent positive pressure ventilation, cardiac massage, sodium bicarbonate and 50 per cent dextrose failed. He developed recurrent convulsions within the first hour and died two hours after birth. Figure 27 shows the changes in pH, heart rate, mean aortic blood pressure and haematocrit in this infant in relation to bicarbonate therapy. This data is not included in the following analysis of results which is based on a uniform dosage schedule of sodium bicarbonate (1.5-4.0 mEq/Kg body weight).

Acid-base Variables

Group I

Figure 28 shows the trends in pH, Pco_2 and base excess during the first hour of life. Fluctuations in pH and Pco_2 were least in Case 6, who was breathing spontaneously. A significant base deficit was present in Cases 3 and 5 at the age of one hour. Arterial Po_2 is not given as the inspired oxygen varied between cases and in the same case at different times. After an hour Cases 4 and 6 were breathing room air with Po_2 values above 80 mm Hg; the Po_2 in Cases 1, 2, 3 and 5 ranged from 59 to 134 mm Hg and the inspired oxygen concentration from 34 to 47 per cent.

Groups II and III

Blood gas and pH determinations before and after treatment with sodium bicarbonate are presented in Tables 35 - 37. Only values obtained immediately before and some ten and thirty minutes following the infusion of alkali are given. Despite the differences in Apgar

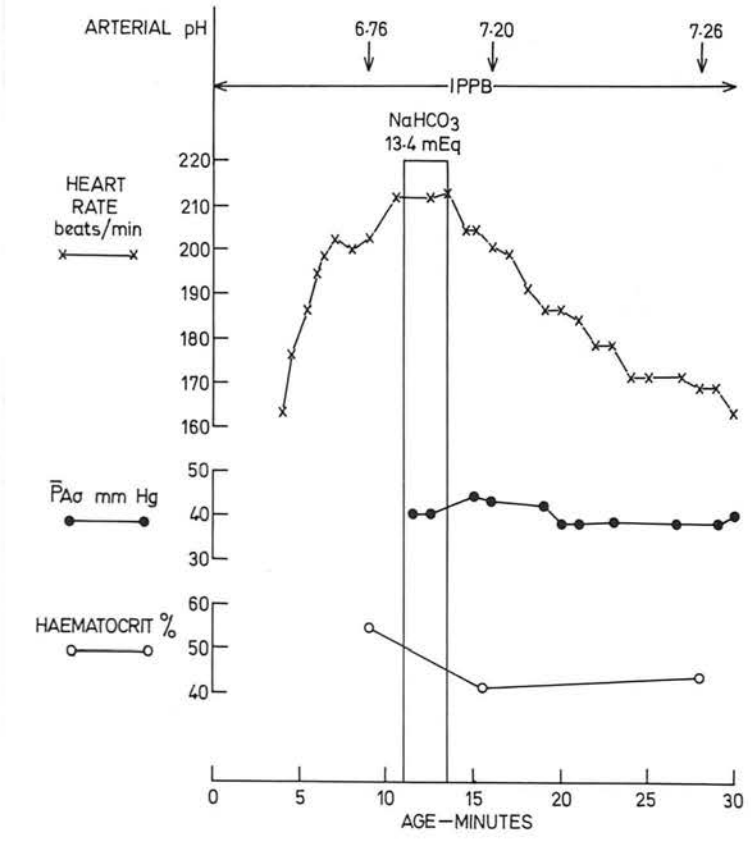

Figure 27

The effect of infusion of alkali on pH, heart rate, mean lower aortic blood pressure and haematocrit (Case 20). Severe intrauterine asphyxia; Apgar score 0 at birth.

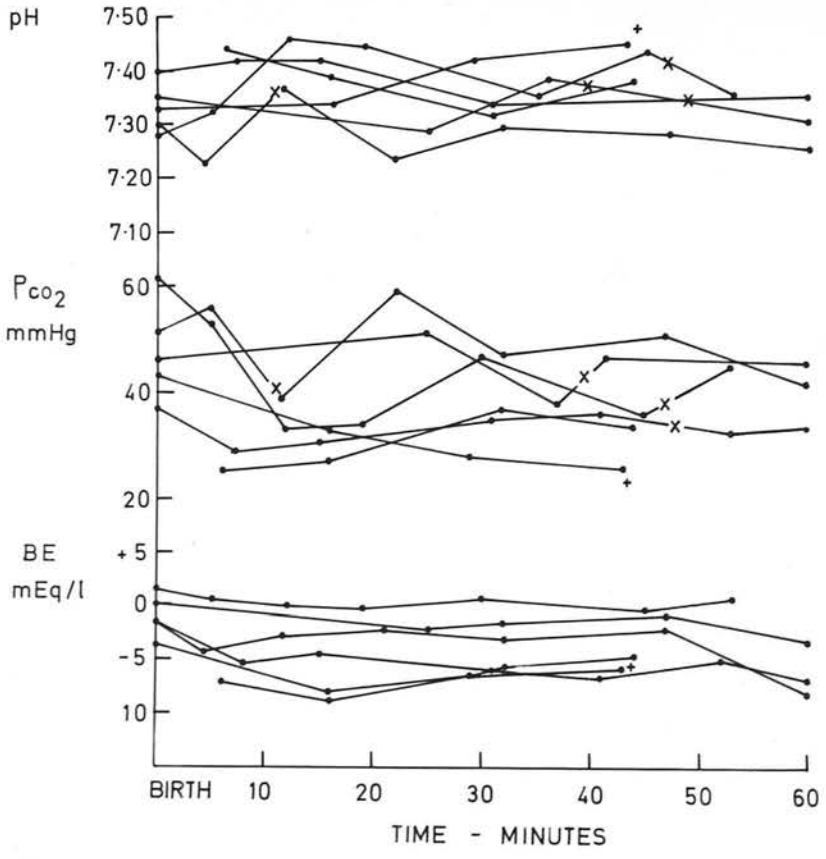

Figure 28

Trends in pH, Pco_2 and base excess during the first hour of life (Group I).

\+ Spontaneous breathing (Case 6)

x Change from IPPB to spontaneous breathing

scores at one minute the pre-bicarbonate acid-base data are similar in both groups. There is a significant increase in pH and base excess in each group following the administration of sodium bicarbonate with the restoration (at least by older child standards) of a normal acid-base status. Figure 29 shows the relationship between Pco_2 and base excess before, and half an hour after the infusion of sodium bicarbonate. A base deficit exceeding 5 mEq/litre persists in two cases (Cases 7 and 17).

Figures 30 and 31 illustrate the sequential changes in Pco_2 and Po_2 in individual patients. An unsustained rise in Pco_2 of 4-11 mm Hg is seen in four patients (Cases 10, 12, 13 and 16). Po_2 on the other hand increased sharply, by 33 and 125 mm Hg in five patients, each of whom had been asphyxiated at birth (Cases 14, 16, 19, 21 and 22). Minute volume was measured and maintained constant throughout the period of study in Case 14. Figure 32 shows the effects of infusion of sodium bicarbonate on blood gas tensions and other variables measured in this patient. A fall in Pco_2 from 47 to 30 mm Hg is accompanied by an increase in Po_2 from 65 to 200 mm Hg.

Cardio-vascular Variables

Group 1

Figure 33 shows the changes in heart rate, mean aortic blood pressure and haematocrit during the first hour. No attempt is made to analyse the trends in heart rate as no consistent pattern emerged. Mean aortic blood pressure fluctuated slightly in artificially ventilated infants, and remained stable when breathing was unassisted (Case 6).

Haematocrit values were remarkably constant - a fall of 3 per cent between 33 and 44 minutes in Case 4 being the largest difference

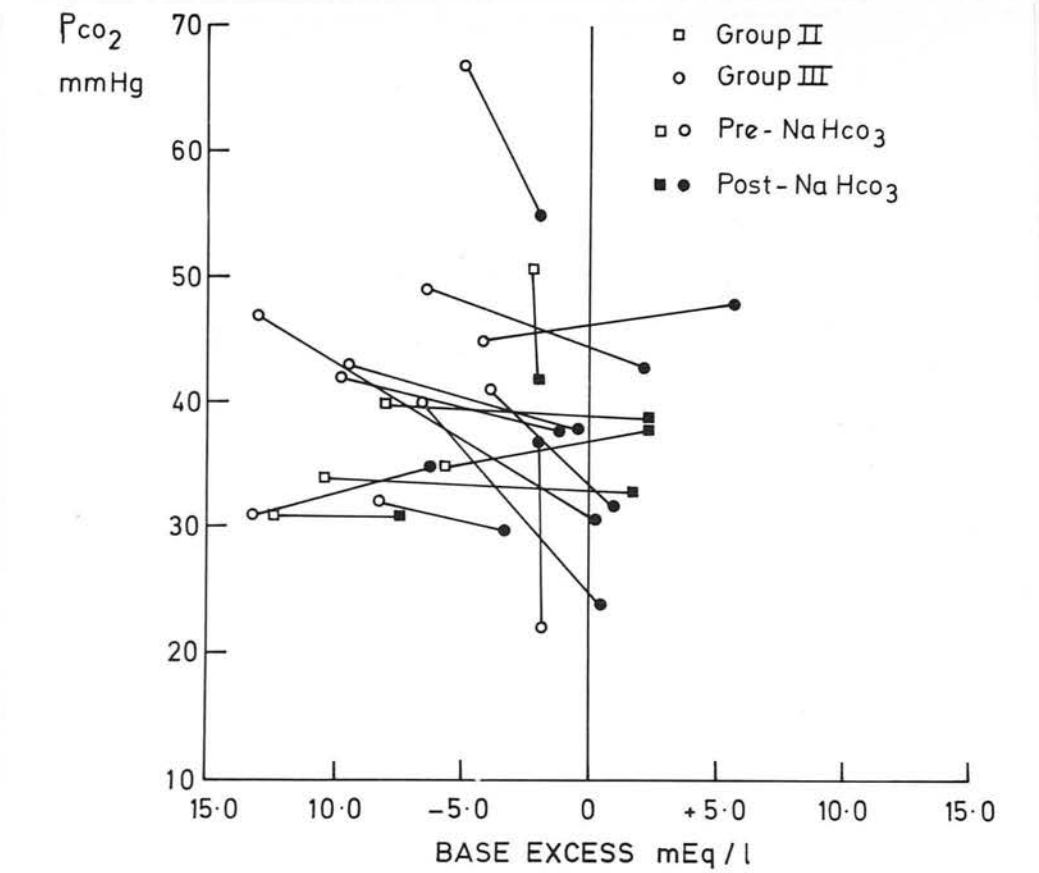

Figure 29

Relation of Pco_2 and base excess before, and half an hour after the infusion of alkali. A base deficit exceeding 5 mEq/l remains in two patients.

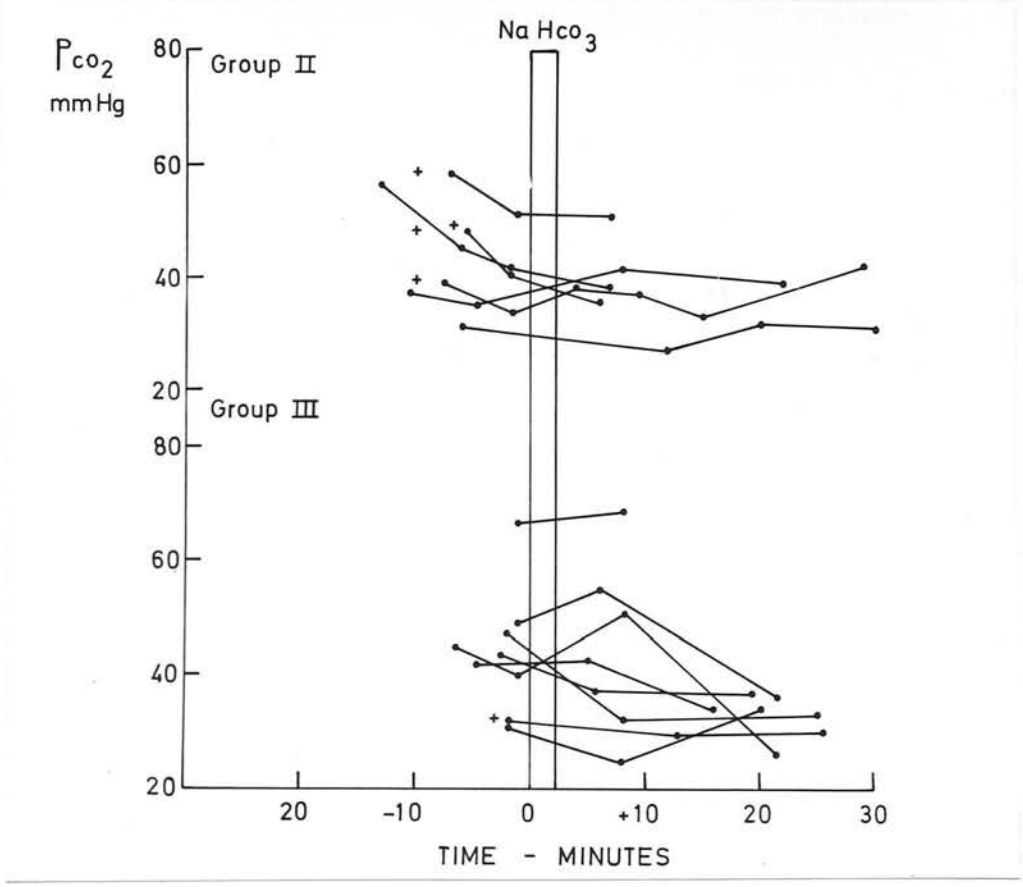

Figure 30

Changes in Pco_2 in relation to sodium bicarbonate therapy. A transient rise in Pco_2 is seen in four patients.

+ Spontaneous breathing throughout period of study

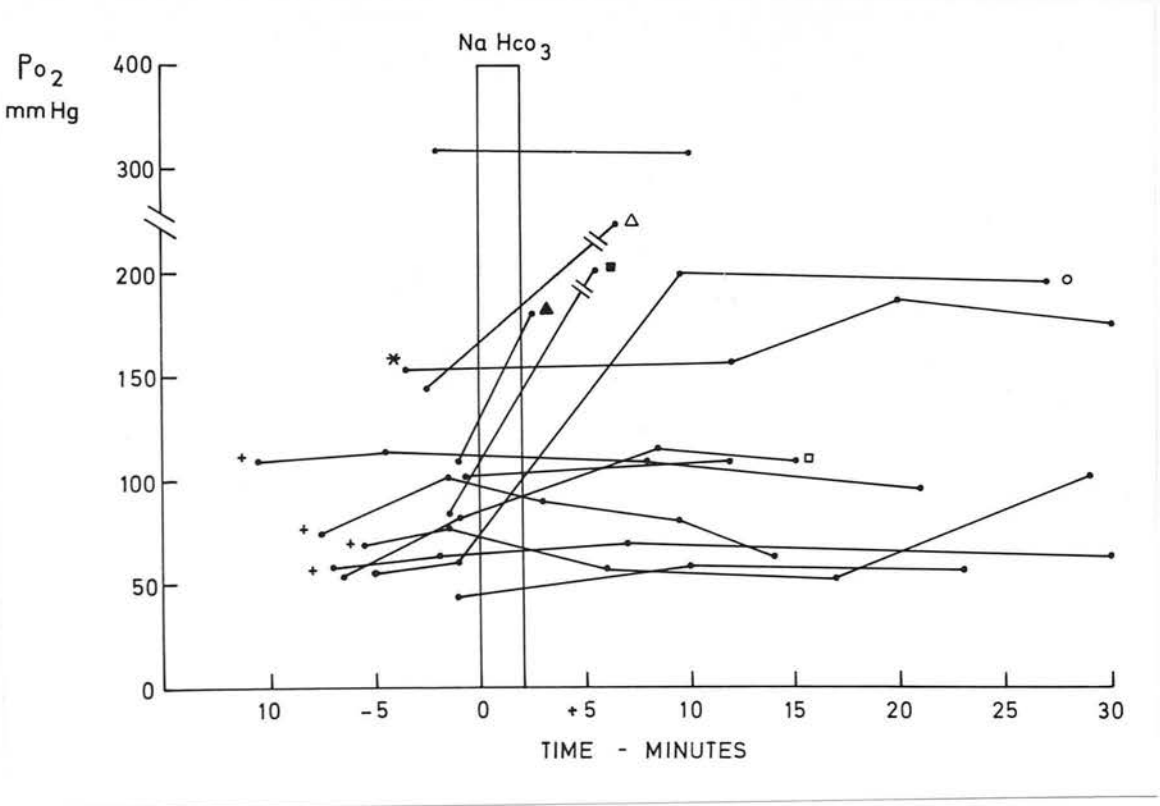

Figure 31

Sequential changes in Po_2 in individual patients in relation to treatment with sodium bicarbonate.

○ Case 14; □ Case 16; ■ Case 19; ▲ Case 21; △ Case 22

\+ Spontaneous breathing throughout period of study

* Pre-infusion FIo_2 reduced from 80 to 60 and then 40 per cent subsequently.

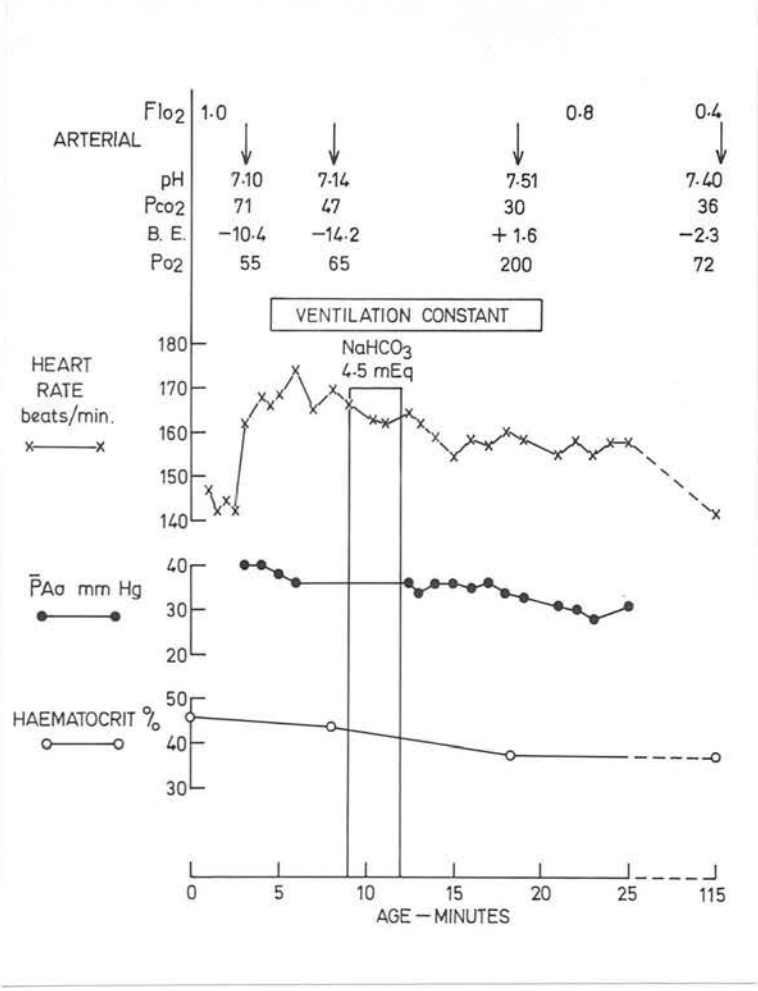

Figure 32

Changes in blood gas tensions, heart rate, mean aortic blood pressure and haematocrit in relation to infusion of base (Case 14). Minute volume was constant throughout the period shown.

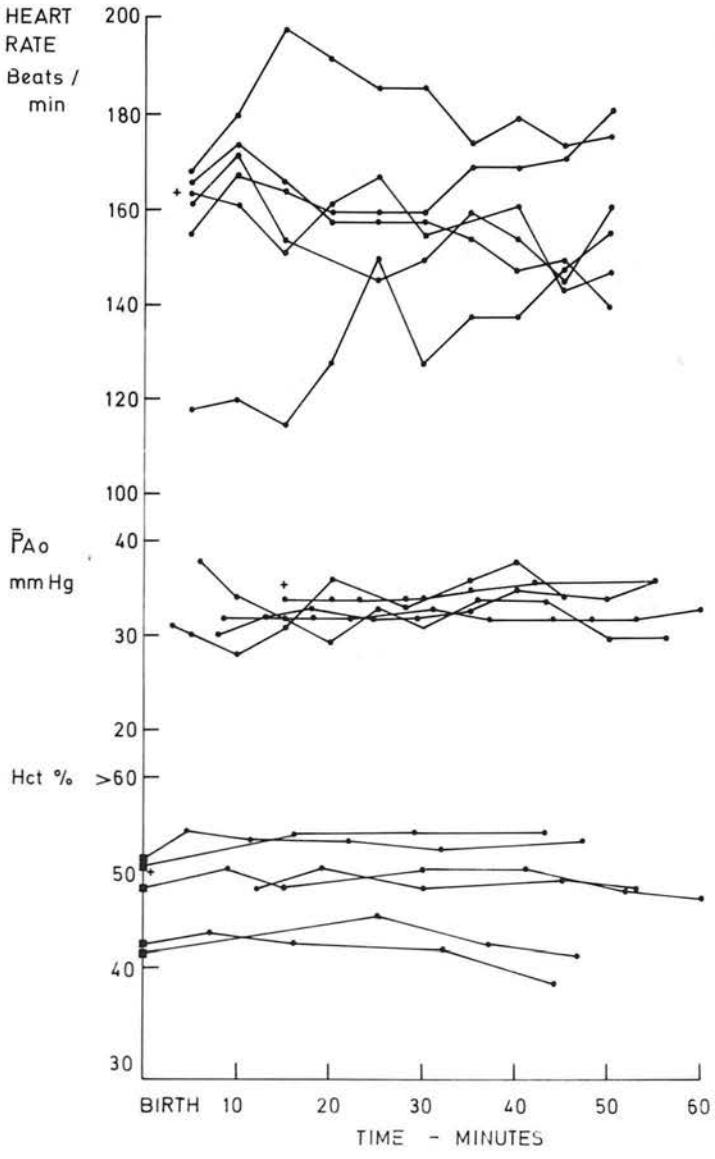

Figure 33

Trends in heart rate, mean aortic blood pressure and haematocrit in the first hour of life (Group I).

+ Spontaneous breathing throughout

■ Cord, umbilical arterial at birth

observed between values in individual cases. Similarly the maximum difference in MCHC was only 1.5 per cent.

Groups II and III

Figures 34 and 35 show the changes in heart rate and mean aortic blood pressure following sodium bicarbonate. Again no consistent trend in heart rate is apparent; in many cases, however, the infusion of alkali was accompanied by an increase, and then a decrease in heart rate. An increase in mean aortic blood pressure (3-10 mm Hg) with a return to pre-bicarbonate levels within a few minutes is seen in Group II. The trend is similar in Group III, where most patients were being ventilated manually. Figure 36 shows the change occurring in Case 18 during inadvertent hyperventilation with IPPR, and treatment with sodium bicarbonate. There is a remarkable fall in blood pressure, with a return to normal when spontaneous breathing is resumed. Sodium bicarbonate had been infused on the basis of the initial blood gas and pH measurements and not those immediately preceding therapy.

The changes in haematocrit following infusion of base are shown in Figures 37 and 38. The trends are similar in each group. When both groups are considered together the fall in haematocrit from pre-bicarbonate value of 50.7 per cent to 45.2 per cent within ten minutes of infusion (Table 38) is not statistically significant. There were no significant changes in the MCHC throughout the period of study.

Electrolyte Concentrations

The blood serum sodium, potassium and chloride concentrations before and after sodium bicarbonate therapy in nine patients are shown in Table 39. Serum sodium concentration exceeded 150 mEq/litre in five patients immediately following infusion. The maximum change in sodium

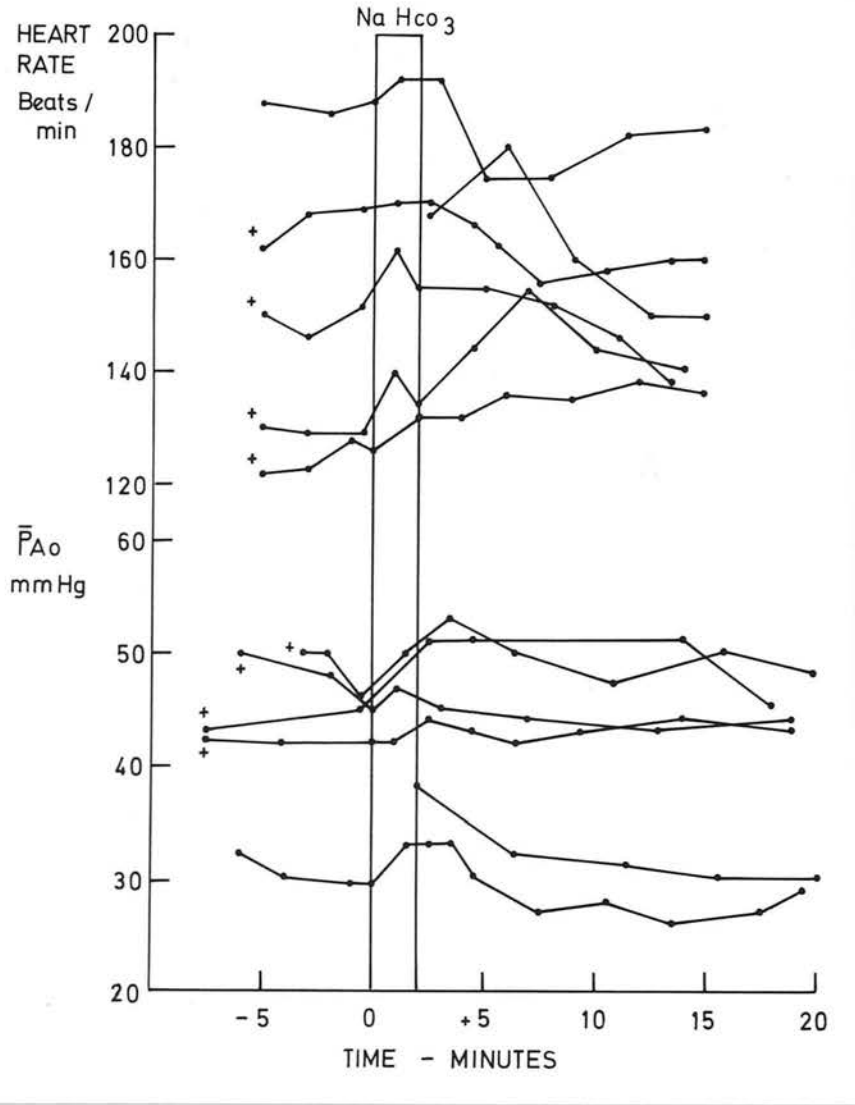

Figure 34

Changes in heart rate and mean aortic blood pressure following the administration of sodium bicarbonate (Group II).

+ Spontaneous breathing throughout

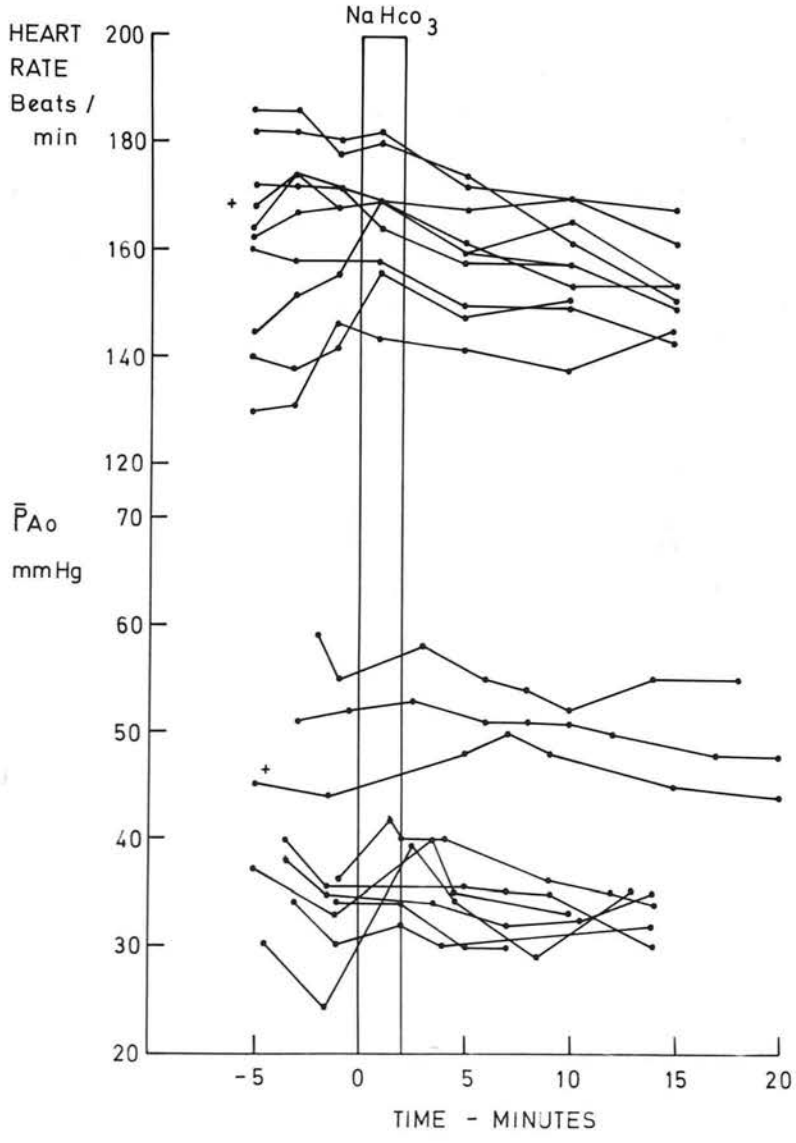

Figure 35

Changes in heart rate and mean aortic blood pressure following the administration of sodium bicarbonate (Group III).

+ Spontaneous breathing at time of study

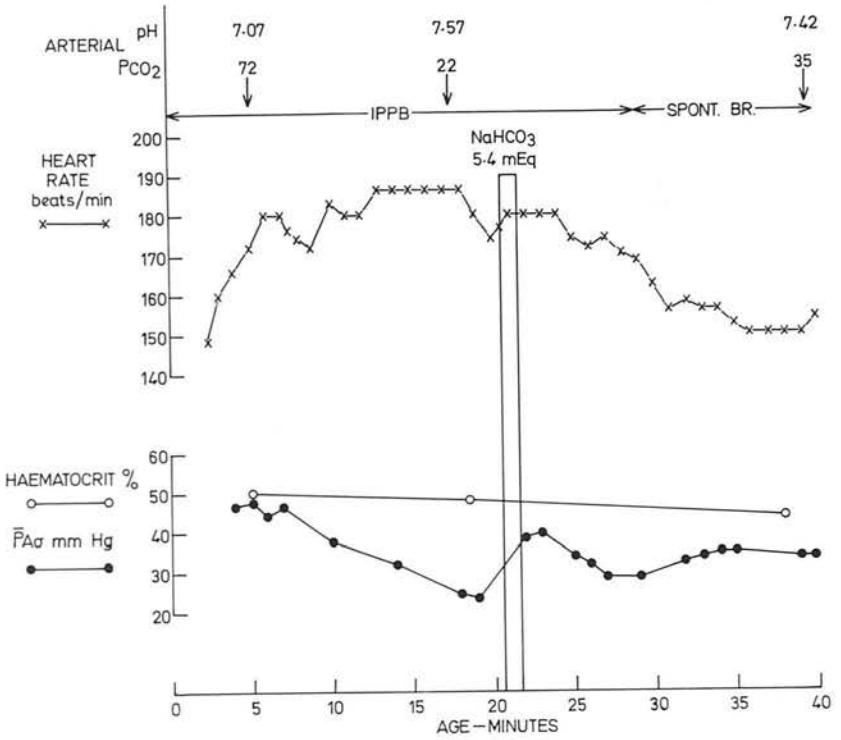

Figure 36

Changes in pH, Pco_2, heart rate, haematocrit and mean aortic blood pressure during IPPB, and in relation to sodium bicarbonate infusion. Severe systemic hypotension occurs during inadvertent hyperventilation. (Case 18)

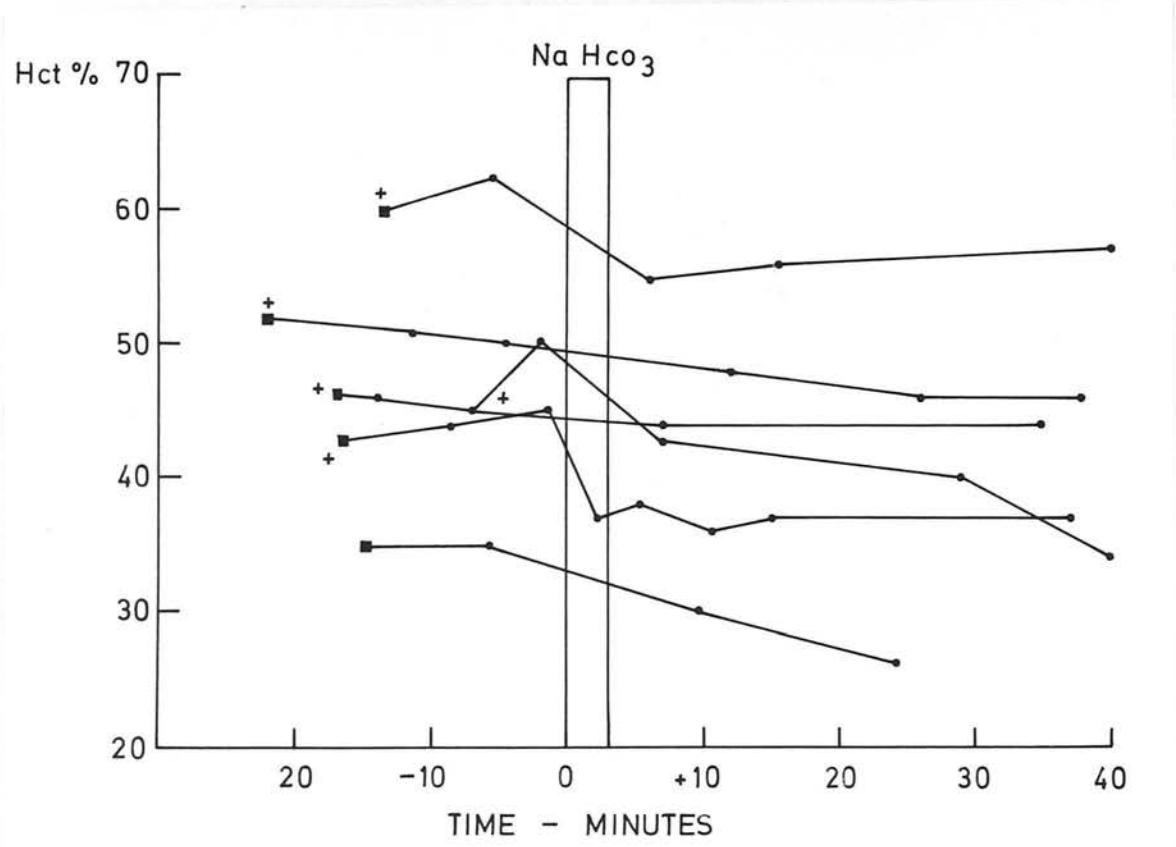

Figure 37

Changes in haematocrit following the administration of sodium bicarbonate (Group II).

+ Spontaneous breathing

■ Cord, umbilical arterial, at birth

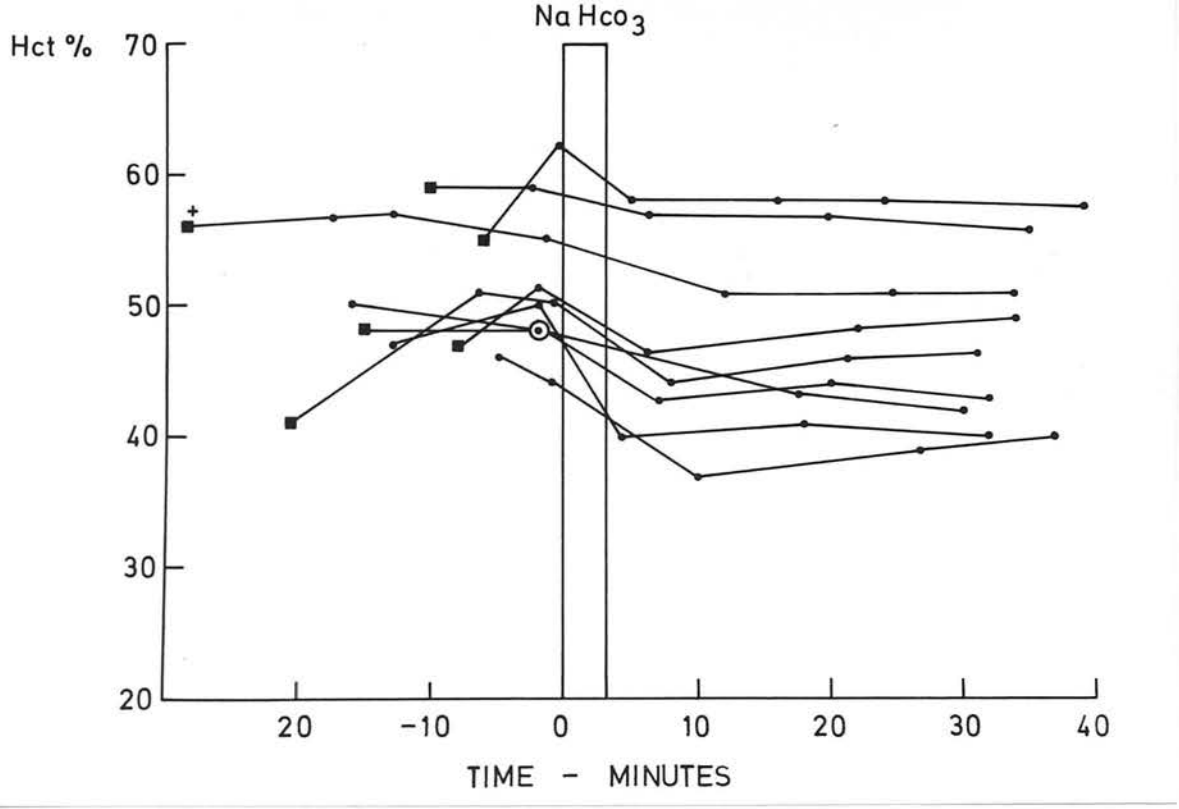

Figure 38

Changes in haematocrit following the administration of sodium bicarbonate (Group III).

+ Spontaneous breathing

■ Cord, umbilical arterial, at birth

concentration 13 mEq/litre (Case 14) corresponds to an osmolar change of 26 mosm/litre. Serum electrolytes were not measured in the one patient treated with 6 mEq/Kg body weight of sodium bicarbonate.

DISCUSSION

The asphyxiated newborn infant suffers from oxygen lack, carbon dioxide retention and decrease in blood pH. The latter is due in part to a rise in Pco_2, but is mainly the result of anaerobic glucose metabolism giving rise to lactic acidosis. When severe, intrauterine or birth asphyxia is a major hazard at any gestational age, but in the pre-term infant it often precedes the development of I.R.D.S. and may well be of aetiological importance by predisposing to pulmonary ischaemia (Chu et al., 1965). Studies in asphyxiated newborn monkeys support the use of alkali and glucose in resusciation (Dawes, 1964; and Adamson, 1964) and it is surprising that this form of treatment, so fully documented in I.R.D.S. (Usher, 1959, 1961; Hutchison, 1962; Gupta, 1965, 1967; Abraham and Brown, 1967; Russell and Cotton, 1968; Sinclair et al., 1968; Stoneman and Owens, 1968; Savignonai et al., 1969) has not been evaluated in the newly born infant.

The timing of clamping the cord and the volume of placental transfusion at birth are likely to have affected the absolute values of several of the measured variables, at least in non-asphyxiated infants, (Usher, Shephard and Lind, 1963; Buckels and Usher, 1965). Studies in foetal lambs following controlled haemorrhage of the ewes suggest that there are no striking changes in cardiac output, or umbilical blood flow in asphyxia (Rudolph, 1969). The distribution of blood between the asphyxiated human foetus and its placenta before or at term is not known however, and the effect of cord clamping on placental transfusions at

birth uncertain. The usual clinical practice of suspending and draining the placenta after the cord has been clamped (Redmond et al., 1965) is likely to be an imprecise and possibly misleading method of estimating residual placental blood volume in this situation.

The acid-base status at birth of infants in Group I was similar to that of many healthy vigorous newborn infants (James et al., 1958) despite the low Apgar score in two patients. The subsequent course of acid-base adjustment in this group (Figure 28) compares with the 'normal' range documented by the studies of Oliver et al. (1966), Weisbrot et al. (1958) and Reardon et al. (1960). Whether these 'normal' values are, in fact, optimal, particularly in the pre-term infant is open to question. The trends observed with pH values near 7.30 and base excess values exceeding 5 mEq/litre might easily be exaggerated following asphyxia (James, 1960; Barnard and James, 1961), and predispose to an increase in pulmonary vascular resistance and right to left shunting of blood - cardinal features of I.R.D.S.

The pre-sodium bicarbonate acid-base status of infants in Groups II and III are not significantly different Co_2 retention having been corrected in Group III patients by intermittent positive pressure ventilation. The effect of infusion of sodium bicarbonate on Co_2 production and excretion has been studied in normal man (Katsaros et al., 1960) and in rabbits (Berg et al., 1969). Provided breathing is adequate the Co_2 formed is quickly eliminated though a transient rise in Pco_2 may occur, as in Cases 10, 12, 13 and 16, (Figures 30 and 31). Berg et al., (1969) cautioned against the use of sodium bicarbonate during apnoea or when breathing is inadequate in view of the risk of increasing intra-cellular acidosis (Adler et al., 1965a and 1965b). No untoward side

effects were observed in any infant, however, during or following treatment with sodium bicarbonate.

The striking increase in Po_2 (Cases 14, 16, 19 and 21) was probably the result of an increase in pulmonary perfusion with improvement in ventilation/perfusion ratios, and a decrease in right to left shunting of blood,as the magnitude of change was greater than would be accounted for by an improvement in ventilation alone. The actual shunt was not quantitated in infants breathing 100 per cent oxygen as arterio-venous oxygen content different had not been determined. A decrease in right to left shunting has been reported in I.R.D.S. following the administration of THAM (Gupta, 1965) and sodium bicarbonate (Russell and Cotton, 1968).

No detailed investigation of the changes in heart rate in the early minutes of life has been reported. In view of the many variables which may affect heart rate during the period, however, the wide range of values was not perhaps surprising. Mean aortic blood pressure in each group was within the normal range for birth weight, and gestational age when compared with the data of Kitterman et al. (1969). The immediate increase in mean aortic blood pressure following the infusion of base may have resulted from improved cardiac output due to a rise in pH or possibly a change in extracellular volume. Diminished peripheral resistance or volume change produced by fluid shifts during the redistribution of sodium could account for the subsequent decline. The questions raised cannot be answered from the data available. Systemic hypotension occurred in only one patient (Case 20) and followed a period of accidental hyperventilation (Figure 36) Blood pressure returned to normal with the resumption of spontaneous breathing.

The haematocrit trends in control infants (Group I) were similar to these seen in normal infants following early clamping of the cord (Usher et al., 1963).

The fall in haematocrit following bicarbonate (Groups II and III) was presumably a dilutional effect following expansion of the extracellular volume as there was no significant change in MCHC to suggest a redistribution of fluid between plasma and red blood cells. In experiments in kittens during which sodium bicarbonate (10 mEq/Kg) was infused over a three minute period, haematocrit fell on average 38 per cent, and MCHC rose by 11 per cent due to red cell shrinkage (Kravath et al., 1970). Changes in sodium and chloride paralleled changes in osmolality and MCHC. The changes in the infants were much less striking in view of the lower dosage regime employed. A sustained fall in haematocrit, as occurs in hypovolaemia in the newborn (Ballard et al., 1972) was not observed.

Finberg (1967) has warned of the danger of "osmole poisoning" and hypernatraemia following the infusion of sodium bicarbonate and has suggested that a rise of 25 m osm/Kg body weight over four hours, is the maximal safe limit of tolerance. The changes shown are well within this limit, which would only be exceeded (theoretically at least) if infusions were repeated more than two or three times in that time period. Only careful follow-up study will reveal whether transient elevation of sodium to above 150 mEq/litre has significant deleterious effect. Behrman (1966) has outlined the other theoretical disadvantages of this form of treatment, but approves its use in appropriate dosage in severely asphyxiated infants (Behrman et al., 1969). Berg et al., (1969) advocate the use of THAM initially in severely asphyxiated and apnoeic infants with the substitution of sodium bicarbonate for THAM as soon as spontaneous or artificial respiration is established. Whether these recommendations, based on studies in non-asphyxiated rabbits, are relevant to the newborn situation is uncertain. The disadvantages of THAM as a

buffer are well recognised (Nahas et al., 1963; Cosby et al., 1964; Goldenberg et al., 1968) and its precise place in the treatment of asphyxia at birth has yet to be defined.

SUMMARY

Serial changes in blood gas tensions, pH, heart rate, mean aortic blood pressure, haematocrit and mean corpuscular haemoglobin concentration (MCHC) were observed in 23 infants during the first hour of life . Three groups of patients were defined. Significant metabolic acidosis was present in two patients in the 'control' Group I at the age of one hour. Mean aortic blood pressure, haematocrit and MCHC in this group remained within the normal range for birth weight and gestational age.

The infusion of sodium bicarbonate, 1-4 mEq/Kg body weight, in Groups II and III resulted in an increase in Po_2, a transient rise in Pco_2 in four patients, and restoration of a 'normal' acid-base status after some thirty minutes. Changes in heart rate were not amenable to precise interpretation. There was an increase in mean aortic blood pressure and decrease in haematocrit following the administration of sodium bicarbonate . An unsustained increase in serum sodium concentrations to 150 mEq/litre or above occurred in five of nine patients in whom serum electrolytes were measured. The calculated osmolar changes following the infusion of alkali are within the tolerance limits at present regarded as being safe.

SECTION VI

LACTATE AND PYRUVATE CONCENTRATIONS IN PNEUMONIA, ASTHMA, CYSTIC FIBROSIS AND CONGENITAL CYANOTIC HEART DISEASE

ARTERIAL LACTATE AND PYRUVATE CONCENTRATIONS IN CHILDREN WITH ACUTE AND CHRONIC HYPOXIA

INTRODUCTION

The degree of asphyxia or oxygen deficiency in infants with pneumonia, asthma and cystic fibrosis has been evaluated in the preceding sections on the basis of clinical signs (pulse rate, respiratory rate and cyanosis), and the measurement of oxygen tension and acid-base status. These methods may fail to register causes of tissue hypoxia other than arterial hypoxaemia. Thus a reduction in oxygen capacity (severe anaemia), inadequate tissue perfusion (shock) or perhaps abnormal oxygen haemoglobin affinity (Duc and Engel, 1969) may result in hypoxia, with a normal Po_2. Huckabee (1958) has appraised anaerobic metabolism in whole animals and in man from measurements of lactate and pyruvate concentrations in the plasma, an approach best appreciated from a consideration of cellular oxidative processes.

Fat, protein and carbohydrate may all end their intermediate metabolic processes by conversion to acetyl coenzyme A, which is then combined with oxalo-acetic acid in Krebs' tricarboxylic acid cycle. In the course of these metabolic activities, and particularly in the operation of Krebs' cycle, $NADH_2$ is produced which links the cycle with the electron transport chain in the cellular mitochondria. Here oxygen is used as the final electron acceptor in the respiratory enzyme chain. $NADH_2$ is oxidised to NAD which is re-utilised for metabolic processes. When, however, the oxygen supply to the interior of the cell is sufficiently diminished, the various cellular oxidation reduction systems shift towards a reduced state. When this happens $NADH_2$ is re-oxidised by pyruvate which is converted to lactate thus -

$$\underset{\text{(pyruvic acid)}}{CH_3\overset{O}{\overset{\|}{C}}COOH} + NADH_2 \rightleftharpoons \underset{\text{(lactic acid)}}{CH_3\overset{OH}{\overset{|}{C}}HCOOH} + NAD \quad (1)$$

Under normal circumstances this equation is displaced to the right. If the equation is re-arranged according to the Law of Mass Action, then -

$$\text{Lactate} = \text{Pyruvate} \times K \frac{NADH_2}{NAD} \quad (2)$$

The concentration of lactate is therefore dependent on the concentration of pyruvate and the constancy of the factor $NADH_2/NAD$ which in turn is dependent on the state of oxidation of the tissue (Huckabee, 1958). If the $NADH_2/NAD$ ratio remains constant, any change in lactate concentration must result from a change in pyruvate concentration and the change will be linear. If, however, the concentration of pyruvate remains stable, any change in the concentration of lactate must reflect a change in the ratio $NADH_2/NAD$. Thus, in tissue hypoxia the ratio of lactate to pyruvate concentration would increase above the ratio normally found during aerobic metabolism.

Olsen (1963) and Alpert (1965) have challenged the validity of this concept in vivo. Since separate pools of $NADH_2$ and NAD exist in the cytoplasm and mitochondria of the cells, the blood lactate pyruvate ratio, which depends upon the cytoplasmic $NADH_2$-NAD system may not reflect the concentrations of $NADH_2$ and NAD within the mitochondrial $NADH_2$-NAD system upon which oxidative metabolism ultimately depends. Moreover, the equilibrium constant K for equation 2. is not the same for blood and tissues, so that differences in absolute concentrations will be obtained. Despite these reservations this concept has proved useful clinically, and conditions associated with tissue hypoxia are characterised by a raised lactate:pyruvate ratio.

In the present study arterial blood lactate and pyruvate concentrations, and lactate/pyruvate ratios in children with acute or chronic hypoxaemia were determined and related to measurements of Po_2 and acid-base variables in corresponding blood samples. Changes occurring during the course of treatment, particularly oxygen therapy, were also investigated.

PATIENTS

Twenty-six infants and children with pneumonia, asthma and cystic fibrosis were included in the study, and blood gas data has been presented for seventeen of these patients in Sections II, III and IV. The remaining cases were investigated after completion of these earlier studies. Studies were also undertaken during the investigation of nine chronically hypoxaemic patients with congenital cyanotic heart disease. Details of these patients are given in Table 40.

Five of the six infants with severe acute pneumonia were too ill to be studied in air, and had breathed oxygen-enriched air for at least thirty minutes before blood samples were taken. In 12 of the 13 patients with asthma, initial measurements were made in air. Prior treatment may have had an important bearing on the results obtained in asthma, and is summarised in Table 41. Of the nine children with severe acute asthma, three had been given oxygen but were removed from their oxygen tents to breathe air for at least twenty minutes before any studies were undertaken. Subcutaneous adrenaline hydrochloride 1:1000 had been given to a further three cases in the preceding two hours. In the remaining children with asthma adrenaline had not been used therapeutically within six hours. None of the acutely ill patients with pneumonia or asthma was receiving intravenous infusion of glucose or electrolytes at the time of study.

Initial studies in the children with cystic fibrosis or congenital heart disease were carried out in air. Tetralogy of Fallot was the most common diagnosis in patients with cardiac disease, none of whom showed signs of cardiac failure or respiratory tract infection.

RESULTS

Of the six infants with severe acute pneumonia, two died (Cases 1 and 2, Table 42). The clinical courses of these two patients are described in detail in Section II, Chapter 2 and Appendix 2. The clinical status of Case 3 was precarious at the outset, but he recovered following treatment with oxygen, antibiotics, digoxin and sodium bicarbonate. Case 4 was treated with antibiotics and made an uninterrupted recovery. Cases 5 and 6 developed severe ventilatory failure and recovered after several days' treatment with IPPB via a Jackson-Rees naso-tracheal tube, using a Loosca ventilator (Air-Shields Ltd.).

The children with asthma, cystic fibrosis and cyanotic heart disease all survived. Details of the asthmatic patients treated with IPPB (Cases 1a, 1c and 12b, Table 41) are presented in Section III, Chapter 2.

The results of initial studies in the different clinical groups are given in Tables 42

Pneumonia

Five of the six infants studied were breathing oxygen (Table 42). Case 2, with a Po_2 of 45 mm Hg breathing 40% oxygen, was the only patient with severe hypoxaemia. The Pco_2 exceeded 50 mm Hg in Cases 1, 4 and 5, and pH was below 7.25 in patients 1, 2 and 3. The base deficit exceeded 5 mEq/litre in Cases 2, 3 and 6, all of whom had elevated blood lactate concentrations. Blood pyruvate concentrations

were raised in Cases 1-4. The highest lactate-pyruvate ratios were found in Cases 3 and 6. Serum transaminase levels measured in Cases 4, 5 and 6, were not significantly raised.

Asthma

Hypoxaemia, sometimes associated with a raised Pco_2 and low pH, was the main blood gas abnormality in the acutely ill patients (Table 43). The blood lactate concentration was above normal in Cases 2, 4 and 7, each of whom had been treated with adrenaline in the preceding two hours. Blood pyruvate concentrations in all but two cases were greater than normal. The highest lactate-pyruvate ratios, 20.8 and 19.8 were found in Cases 1c and 4 respectively. The lowest lactate-pyruvate ratios (7.5 and 8.5) were found in Cases 3 and 6, who had been treated with oxygen for several hours prior to sampling. Serum transaminase levels in three patients were within normal limits.

Moderate metabolic acidosis was the main abnormality in the three patients (Cases 10, 11 and 12) who were not acutely ill. Arterial lactate and pyruvate concentrations were unremarkable.

Cystic Fibrosis

Results of initial studies in children with cystic fibrosis are shown in Table 44. Case 1, with a Po_2 of 50 mm Hg was the only patient with severe hypoxaemia. Pco_2 exceeded 50 mm Hg in Cases 1, 2 and 4. pH was not significantly reduced in these cases due to the compensatory increase in bicarbonate as shown by the positive values of base excess. The blood lactate concentration was above normal in Case 1 (3.39 mM) and within normal limits in the remaining cases. Blood pyruvate concentrations were raised in Cases 1, 3 and 6. The lactate-pyruvate ratio was 23.1 in Case 1, and probably within normal limits in Cases 2-6.

Cyanotic Congenital Heart Disease

Hypoxaemia, an increase in alveolo-arterial oxygen tension gradient, and polycythaemia were the main findings in the nine children with congenital heart disease (Table 45). pH was normal in Cases 2-9, and slightly reduced in the remaining case. The Pco_2 was below normal in Case 4, but within normal limits in the remaining cases. There was a slight reduction in base excess in Cases 1, 3, 4, 7 and 8. The blood lactate concentration was at the upper limit of normal in Case 3 (2.0 mM) and markedly raised in Case 9 (6.66 mM). The blood pyruvate concentration was above normal in all but Case 5. The lactate-pyruvate ratio was strikingly elevated in Case 9 (L:P = 54.6). Arterial oxygen content ranged from 12.7 to 25.0 vols. per cent.

Effects of Therapy

The effects of oxygen therapy on the blood gas tensions and pH of children with pneumonia, asthma, and cystic fibrosis have been described in Sections II, III and IV. The changes in blood lactate and pyruvate concentrations during treatment are summarised in Table 46. The concentrations of lactate and pyruvate tended to fall following oxygen therapy, even when initial levels were within normal limits. These changes, shown in Figure 39, were statistically significant for pyruvate ($0.05 > P > 0.02$) but not for lactate ($0.10 > P > 0.05$).

The effects of infusion of sodium bicarbonate in patients with pneumonia and asthma are difficult to interpret, as there was often a concurrent rise in inspired oxygen concentration. The most striking change occurred in Case 12b. Lactate and pyruvate concentrations rose following the infusion of bicarbonate without significant change in

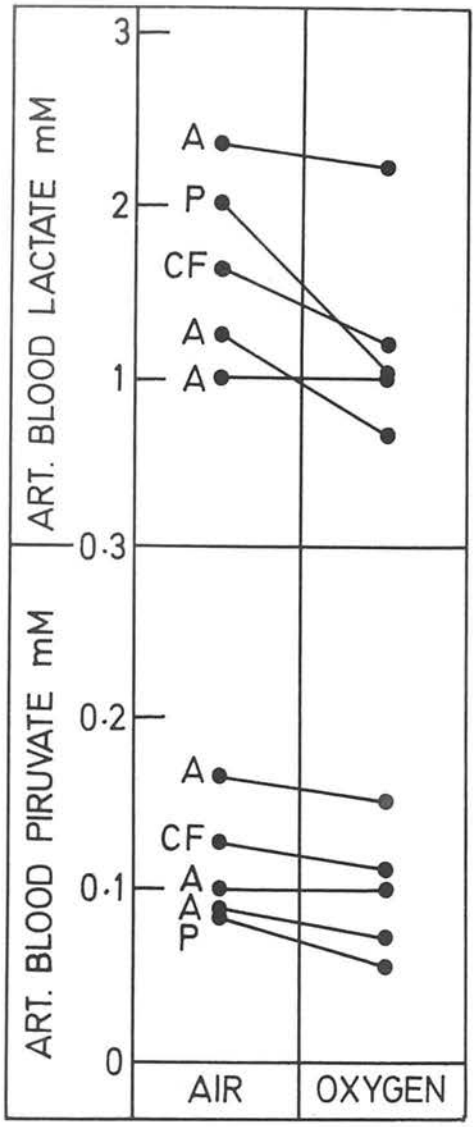

Figure 39

Changes in arterial blood lactate and pyruvate concentrations following the administration of oxygen.

A - Asthma; P - Pneumonia; CF - Cystic Fibrosis

There is a significant fall in blood pyruvate concentration ($0.05 > P > 0.02$)

the lactate-pyruvate ratio. The inspired oxygen concentration had been increased from 35 to 74 per cent, and was associated with a dramatic rise in Pco_2 and slight fall in pH.

The effects of ether and possibly hypotension are best seen in Case 1a, a patient in status asthmaticus who had been anaesthetised with ether and treated with IPPB for severe ventilatory failure. There was an increase in lactate and pyruvate concentrations, and in the lactate-pyruvate ratio. This patient's clinical course is outlined in Section III, Chapter 2.

In cyanotic congenital heart disease (Table 47) the administration of 80-100 per cent oxygen produced a slight increase in Po_2 without significant change in Pco_2 and pH. The associated rise in arterial oxygen saturation and arterial oxygen content was particularly striking in Cases 4 and 7. Figure 40 suggests that a reduction of lactate and pyruvate concentration occurred during oxygen therapy. The most impressive change occurred in Case 9, following two days' continuous treatment with 50-70 per cent oxygen. These changes were not statistically significant.

DISCUSSION

The results present an opportunity to assess the importance of lactic acid accumulation as a cause of acidosis in patients with acute and chronic hypoxia, and to discuss the clinical relevance of measurements of arterial lactate and pyruvate before and after treatment. Oliva (1970) has reviewed the principal causes of lactic acidosis, some of which may be relevant in these cases.

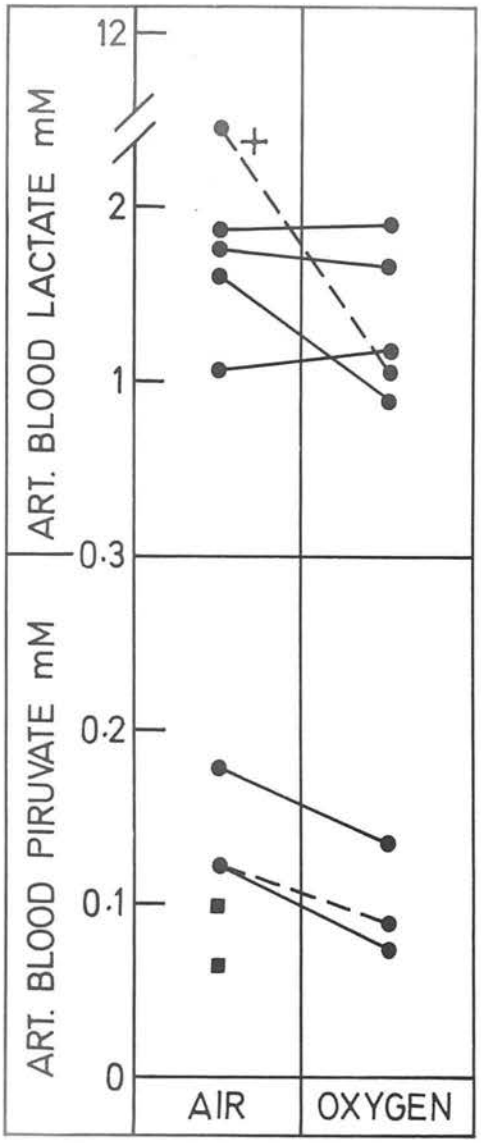

Figure 40

The effect of breathing 75-100 per cent oxygen for thirty minutes on the arterial blood lactate and pyruvate concentrations in congenital cyanotic heart disease.

+ Before and after forty-eight hours in oxygen

■ No figures available during treatment with oxygen

Hypoxaemia

During acute hypoxaemia moderate increases in lactate occur in animals and in man (Huckabee, 1958; Eldridge, 1966; Daniel et al., 1966). The markedly raised blood lactate levels in pneumonia (Cases 2 and 3, Table 42) are likely to have been caused, in part at least, by this mechanism. Both patients had been in oxygen for thirty minutes when initial blood samples were obtained. Case 2, Po_2 45 mm Hg, remained severely hypoxaemic, in Case 3 the Po_2 rose to 220 mm Hg. The degree of hypoxaemia in the infants prior to treatment with oxygen is not known. The same mechanism may explain the lactic acidosis in cystic fibrosis (Case 1, Table 44). Most of the patients with asthma and the remaining cases of cystic fibrosis were only moderately hypoxaemic breathing air, so that normal lactate and pyruvate concentrations were not unexpected. Huckabee (1958) found that the inhalation of low oxygen mixtures in human subjects did not result in a marked increase in lactate until the arterial Po_2 was less than 35 mm Hg.

Lactic acidosis does not usually accompany chronic hypoxaemia (Huckabee, 1965; Eldridge, 1966). In congenital cyanotic heart disease (Table 45) Po_2 varied from 24-55 mm Hg. A marked increase in lactate: pyruvate ratio occurred in only one patient (Case 9) with a Po_2 of 27 mm Hg and Hb 19.8 g per cent. Severe hypoxaemia resulting in tissue hypoxia is the likeliest explanation for this finding. In the remaining cases compensatory mechanisms, particularly polycythaemia, presumably account for the relatively normal lactate/pyruvate findings.

Hyperventilation

Increased blood lactate concentrations have been found consistently during passive hyperventilation under anaesthesia in animals (Anrep and Cannon, 1923) and in human subjects (Papadopoulos and Keats, 1959;

Sykes and Cook, 1965; Chamberlain and Lis, 1968). The levels of lactate during passive ventilation from 1-4 hours have ranged from 1.20-3.0 mM. The lactate:pyruvate ratio has generally been increased. Similar but more striking findings have been reported in certain pathological conditions associated with prolonged hyperventilation. Huckabee (1961) described six patients with prolonged hyperventilation who had lactate levels of 10-22 mM, but none were acidotic (pH 7.47-7.61). Dossiter et al. (1965) described two patients with prolonged hyperventilation due to Wernicke's encephalopathy, who had high lactate levels without acidaemia. Field et al (1966) report similar findings in acute leukaemia. In Reye's syndrome in which encephalopathy co-exists with fatty degeneration of the liver, the serum lactate and lactate:pyruvate ratio may be markedly increased (Simpson, 1972). Hyperventilation may have contributed to the lactic acidosis seen in two patients with pneumonia (Cases 3 and 6, Table 42) with Pco_2 levels of 29 and 30 mm Hg respectively. There was, however, no correlation between Pco_2 and lactate or pyruvate in any of the clinical groups investigated.

"Shock"

The occurrence of lactic acidosis in cardiogenic, haemorrhagic and septic shock is well recognised (Mackenzie et al., 1964; Tranquada et al., 1965; Peretz et al., 1964; Hopkins et al., 1965; and McLean et al., 1967). Lactic acidosis may occur early in shock and precedes other clinically recognisable signs of shock (Peretz et al., 1964). Pneumonia Case 6 was not clinically shocked on admission, but showed an elevated blood lactate concentration without striking abnormalities in blood gas tension or pH. She developed severe circulatory collapse some two

hours later, the pH falling to 6.91 and the Pco_2 rising to 125 mm Hg. This patient was resuscitated and recovered after several days' treatment with IPPB. Shock may also have contributed to lactic acidosis in Cases 2 and 3, (Table 42) both of whom showed clinical signs of severe shock on admission to hospital.

Role of the Liver

The role of the liver in lactic acidosis has been stressed by Berry (1967) who suggests that lactate accumulation during shock and during hyperventilation is not only due to over-production of lactate by extra-hepatic tissues, but also to a great extent to under-utilisation by the liver secondary to a decrease in splanchnic and hepatic artery perfusion. Under such conditions the liver may change from a major organ of lactate uptake, to one of lactate production. There is also evidence that severe acidosis (pH 7.1) per se may reduce hepatic uptake of circulating lactate (Hems et al., 1966) and thus compound the lactic acidaemia. Whether these mechanisms were operative here is uncertain. The normal serum transaminase levels obtained in several patients with pneumonia and asthma suggest that liver function is usually normal in these conditions. Unfortunately, transaminase levels were not determined in the two infants with pneumonia, Cases 2 and 3 (Table 43) in whom lactate levels of 14.25 and 5.01 mM respectively, were found.

Effects of Adrenaline

Three of the nine acutely ill patients with asthma had a Po_2 below 50 mm Hg (Table 43) and in two of these, blood lactate and pyruvate concentrations were within normal limits. The highest lactate levels were seen in Cases 2, 4 and 7, but only Case 4 showed an increase in the

lactate:pyruvate ratio. The use of subcutaneous adrenaline before sampling may account for these findings. Bearn (1951) and Greene (1961) have demonstrated raised lactate concentrations in normal man following infusion of adrenaline. No studies have been reported describing the effect on blood lactate concentration of repeated injections of adrenaline subcutaneously in asthmatic patients. Tolstoi (1921), however, reported an increase in venous lactate level to 3.5 mEq/litre in normal subjects following the subcutaneous administration of 15 minims of adrenaline, which suggests that similar findings are likely in asthma. The increased lactate levels may be due to the glycogenolytic effect of adrenaline, and any increase in lactate:pyruvate ratio to the effects of tissue hypoxia, perhaps due to increased oxygen requirements (Ellis, 1956) or to a preponderance of the vasoconstrictive over the vasodilator effects of adrenaline. It is unlikely that hepatic uptake of lactate is impaired, for the administration of adrenaline even in small doses enhances hepatic blood flow in man (Bearn, 1951). This is supported by the normal transaminase levels in four asthmatic patients (Table 43).

Effects of Therapy

The tendency for lactate and pyruvate concentrations to fall during oxygen therapy in acutely hypoxaemic patients is not surprising in view of the increases in Po_2. In certain other patients (Cases 3 and 6, Table 46) the low concentrations of lactate and pyruvate on admission may have resulted from prior oxygen therapy. It is interesting to speculate whether the normal lactate and pyruvate concentrations in Case 1 (Table 42) and Case 6, during the follow-up, (Table 46) were the result of treatment with oxygen. Case 1 died within a short time of measurements being made, and Case 6 developed severe cardio-respiratory

collapse which would have been lethal had immediate facilities for treatment not been available. In these cases measurements of lactate and lactate:pyruvate ratio did not correlate with clinical severity.

The mechanism of lactate production by sodium bicarbonate is not clear (MacLeod et al., 1917; Haldi, 1933; Tobin, 1964). Gevers and Daudle (1963) suggest that it is due to an increase in glycolysis either due to release of a rate-limiting step in the glycolytic pathway, or in some tissues to a block in the citric acid cycle with subsequent stimulation of glycolysis. THAM has been shown to have a similar effect on lactate production, suggesting that the effect of bicarbonate is due to alkalosis and not the bicarbonate ion itself (Tobin, 1964). In Case 12b (Table 46) however, the increases in lactate and pyruvate following infusion of bicarbonate were associated with a slight fall in pH due to the simultaneous increase in Pco_2, from 78 to 125 mm Hg.

Accumulation of lactate during ether anaesthesia in dogs and in human subjects (Greene, 1960) has been ascribed to the release of adrenaline. In patient 1c (Table 45) the increase in lactate from 1.94 mM to 7.79 mM following ether anaesthesia, may have been in part due to hypotension, and possibly the rapid decrease in Pco_2 which occurred within a short period after starting mechanical ventilation. Liver dysfunction may also have contributed as the SGPT increased from 21 to 39 SF units and SGOT from 51 to 92 SF units following ether anaesthesia. Significant changes in lactate and pyruvate ratio do not occur after nitrous oxide (Greene, 1960) or halothane anaesthesia (Lowenstein et al., 1964), which raises the question of the suitability of ether in this situation.

SUMMARY

Arterial blood gas tensions, pH, and lactate and pyruvate concentrations were measured in children with acute and chronic hypoxia. A high level of lactate, often with an increase in lactate:pyruvate ratio, may occur in acutely hypoxic children with severe acute pneumonia, and during exacerbations of infection in cystic fibrosis. In acute asthma, where moderate hypoxaemia is usual, an increase in blood lactate concentration and lactate:pyruvate ratio may result from recent treatment with adrenaline. In chronic hypoxaemia, lactate concentrations are usually within normal limits.

There is a significant fall in blood pyruvate, following the administration of oxygen, in acute hypoxaemia. The infusion of sodium bicarbonate in acute respiratory acidosis may result in a moderate increase in blood lactate without change in lactate:pyruvate ratio. The administration of ether in status asthmaticus may cause severe lactic acidosis and an increase in lactate-pyruvate ratio.

The many factors which affect the concentration of lactate and pyruvate in these clinical situations render interpretation difficult, and detract from the importance of such measurements in routine clinical practice.

S E C T I O N V I I

OXYGEN CONCENTRATIONS IN TENTS AND INCUBATORS

OXYGEN CONCENTRATIONS IN TENTS AND INCUBATORS IN PAEDIATRIC PRACTICE

Oxygen is usually administered in paediatric practice by commercially available tents or incubators. In addition to the regulation of oxygen concentration of the inspired gas, these must provide for the control of temperature and humidity, and the disposal of carbon dioxide. The present report, published previously (Simpson and Russell, 1967) is concerned with the concentrations of oxygen attainable in commonly used tents and incubators. Other aspects of their performance have been thoroughly evaluated (Chamney, 1969; HMSO 1969; Hey, 1971).

Oxygen concentrations of at least 60 per cent are claimed for many of their products by the manufacturers of tents and incubators, tested under laboratory conditions. As an inspired oxygen concentration of 40 per cent does not always relieve hypoxaemia in infants with acute respiratory failure (Downes and Striker, 1966; Simpson and Flenley, 1967), it seems relevant to report the oxygen concentrations attainable in present-day tents and incubators, both in ideal circumstances, and during routine clinical use.

Tents and Incubators

Six tents (Table 48) and four models of incubator (Table 49) were studied. Tents 1 (Air-Shields Type D Croupette), 2 (Air-Shields Universal Croupette), and 3 (Oxygenaire Humidaire Tent) are used for infants and young children, whereas Tents 4 (Oxygenaire Universal Tent) and 5 (Oxygenaire Mark V Tent) are more suitable for older children who may find the others too confined. A high humidity is provided by each except Tent 4, but coolness for fevered children is obtainable in all. Tent 6 (Oxygenaire Venturi Head Tent) is designed to provide controlled

oxygen therapy to adults with chronic respiratory insufficiency, during exacerbations of infection.

The incubators (Table 49) are used in the neonatal period and provide high humidity and accurate temperature control in addition to oxygen. The Air-Shields Intensive-Care Isolette and the Oxygenaire New Incubator are fitted with a device to limit oxygen concentration to 40 per cent or less, though higher concentrations are possible when necessary. The Oxygenaire Series III Incubator is included in this study as it is still widely used. The Oxygenaire Mark III Portable Incubator is generally used to transport newborn infants from home to hospital, thereby minimizing the risk of hypothermia and/or hypoxia during the journey.

PROCEDURE

The tents and incubators were tested under normal working conditions. In Tents 1 to 4 the patients were infants or young children believed on clinical grounds to require oxygen therapy, whereas healthy children co-operated in testing Tents 5 and 6. The canopies of Tents 1 to 5 were carefully tucked in to avoid leakage and all zips were tightly closed. Each tent was then flushed as recommended (usually 10 litres of oxygen per minute for 30 minutes) and the oxygen flow rate subsequently adjusted to 2, 4, 6, 8, 10, and 20 l/min. The oxygen flow meters used were supplied by the British Oxygen Company and are calibrated from 0 to 10 l/min. A dual outlet regulator was used to provide flow rates of 20 l/min. Samples of inspired gas were taken from within 1 in (2.5 cm) of the child's mouth after 20 minutes at each flow rate into 100-ml lubricated glass syringes via stiff rubber tubing introduced through a small aperture in each tent. In this way samples were

obtained under ideal clinical conditions. Tent 6 did not require flushing, and was sampled at oxygen flow rates of 2, 4, and 6 l/min.

Tents 1 to 4 were also sampled at random on numerous occasions. These tents were invariably flushed before initial usage, but routine reflushing after feeding or other interference was often omitted. The incubators were tested during use without previous flushing, every precuation being taken to avoid leakage. Most of the random measurements were made by Nurse D J Russell.

RESULTS

The oxygen concentrations attained in tents under ideal clinical conditions are shown in Table 48. An oxygen concentration exceeding 50 per cent was attained in Tents 1, 3, 4, and 5 at a flow rate of 10 l/min., whereas 31 per cent was the highest concentration attained in Tent 2 at a similar flow rate. With close apposition of the inner and outer tanks of the ice-box, possible after subsequent modification, by Air-Shields Limited of the canopy of Tent 2, an oxygen concentration of 45 per cent was obtained after one hour at a flow rate of 10 l/min. The oxygen concentrations in Tents 1, 3, and 6 are close to those claimed possible by their manufacturers, while the levels in Tent 5 are similar to those published by Freedman (1964).

The results of random sampling (Tents 1 to 4) are shown in Figures 41-44. When Tent 1 is used as recommended with the pressure gauge in the "green area" (usually 6 l/min), oxygen concentrations of 30 to 45 per cent are achieved (Figure 41). Higher concentrations (by 4-6 per cent) are possible when the ice-box is covered. Similarly, higher oxygen concentrations are attained in Tent 2 when the ice-box is sealed over with polyethylene (Figure 42). This improves contact between the outer

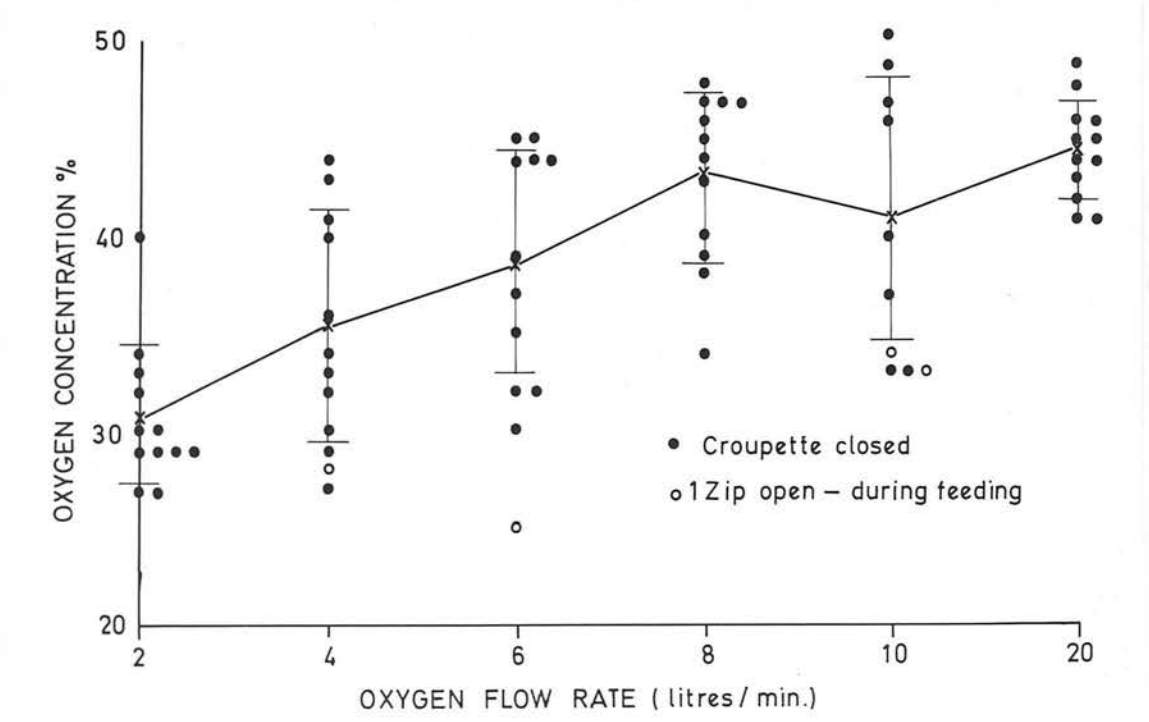

Figure 41

Concentration of oxygen ($\pm$ 1 S.D.) achieved in Air-Shields Type D Croupette in relation to flow of oxygen (random measurements).

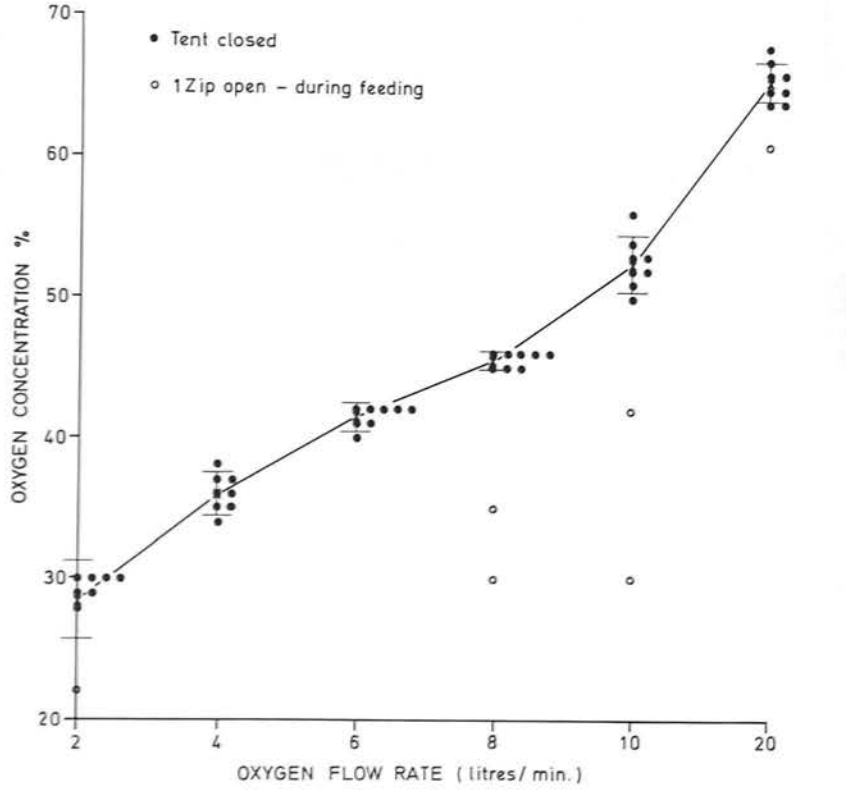

Figure 43

Concentration of oxygen ($\pm$ 1 S.D.) achieved in Oxygenaire Humidaire Tent in relation to flow of oxygen (random measurements).

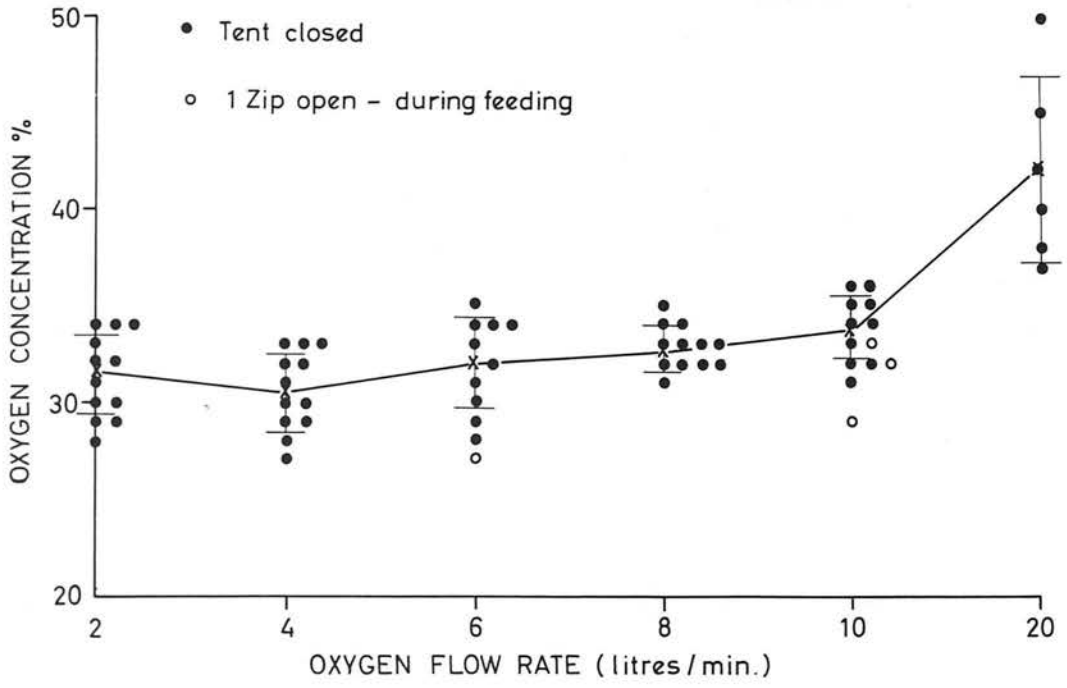

Figure 44

Concentration of oxygen ($\pm$ 1 S.D.) achieved in Oxygenaire Universal Tent in relation to flow of oxygen (random measurements).

and inner ice-tanks, where leaks may be associated with considerable air indrawing due to the Venturi circulation at that point. In Tent 3 an oxygen concentration of 40 per cent is readily achieved at a flow rate of 6 l/min. (Figure 43) whereas a flow rate of 20 l/min. is required to produce a similar concentration in Tent 4 (Figure 44). The mean oxygen concentrations, ideal and random, in Tents 1 to 4 at oxygen flow rates of 10 l/min. are shown in Figure 45. Oxygen concentrations greater than 50 per cent are invariably attained in Tent 3.

Table 49 shows the oxygen concentrations measured in incubators and relates them to their manufacturers' recommendations.

COMMENT

The oxygen requirements of hypoxic children may vary greatly, and depend on the cause and severity of the hypoxia.

These findings are, however, in general agreement with those of Batson and Young (1958) who state that they were "unable to create and maintain therapeutic concentrations of oxygen in tents", in routine practice.

The principles underlying rational oxygen therapy have been reviewed (Brit. med. J., 1964), and Flenley (1967) has emphasised that oxygen therapy should aim to provide an adequate partial pressure of oxygen at the cellular mitochondria. It is probably that in many instances an oxygen concentration of 50 volumes % - that is, the standard recommended for tents by the Committee on Public Health Relations of the New York Academy of Medicine (1950) - fulfils this condition. While this concentration of oxygen may be dangerous to premature babies, such babies are generally nursed in incubators in which special provision is made

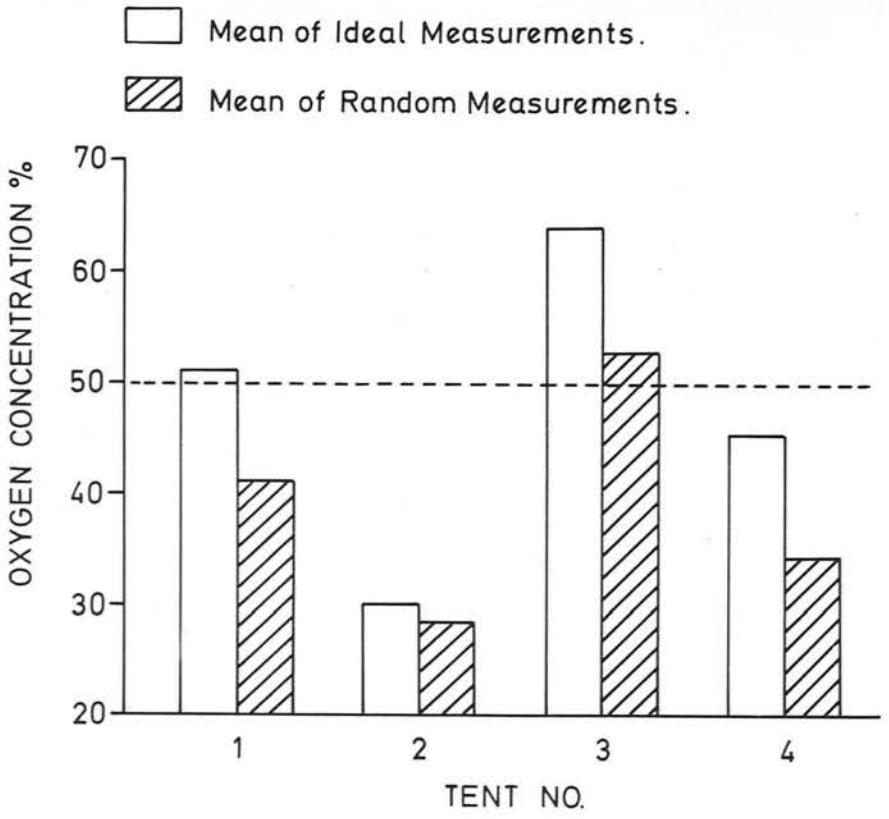

Figure 45

Oxygen concentrations in Tents 1 (Air-Shields Type D Croupette), 2 (Air-Shields Universal Croupette), 3 (Oxygenaire Humidaire Tent), and 4 (Oxygenaire Universal Tent) at an oxygen flow rate of 10 l/min. Comparison of means of ideal and random measurements.

to regulate the ambient oxygen concentration to under 40 per cent (Table 49) thus minimizing the risk of retrolental fibroplasia. Furthermore, the use of high oxygen concentrations in the treatment of chronically hypoxic children with hypoventilation may produce carbon dioxide narcosis (Bruck, 1957). There is, however, little risk of precipitating respiratory depression by this means in infants with acute lower respiratory tract infections (Reynolds, 1963; Simpson and Flenley, 1967). The main use of oxygen tents and croupettes is probably in the treatment of such cases, in which an inspired oxygen concentration of 40 per cent or more may be necessary to ensure a normal arterial oxygen tension (Po_2) (Simpson and Flenley, 1967). This requirement is most likely to be met in Tent 3 (Figures 43 and 45) in which an oxygen concentration of 50 per cent is attainable at a flow-rate of 10 l/min. In apparatus of more recent design (Wayne and Chamney, 1967; Gomez et al., 1968) a concentration of 50 per cent is readily achieved at a lower flow-rate of oxygen.

In asthma or chronic respiratory insufficiency in infancy and childhood the place of oxygen therapy has yet to be defined precisely, though the risks of injudicious oxygen therapy to children with cystic fibrosis of the pancreas are recognized (Bruck, 1957). The importance of controlled oxygen therapy in adult practice is fully recognised (Hutchison et al., 1964; Campbell, 1967; Schiff and Massaro, 1967; Smith et al., 1967; Eldridge and Gherman, 1968). The Edinburgh Mask (Flenley et al., 1963), at 2 litres of oxygen per minute, the Ventimask (Campbell and Gebbie, 1966) and Tent 6 described here, all deliver about 30 per cent oxygen. The latter is sometimes of value in children, but some young children, apprehensive and fighting for breath, find it too confined. The children who helped in testing this tent (aged 7-9 years) were fully at ease within a few minutes.

The indications for oxygen therapy in the newborn have been reviewed by Roberton et al., (1968). Incubators are generally used in this period and are seldom appropriate for infants over 2-3 months of age. The recognition that retinal damage in premature babies is related more to a high arterial oxygen tension than the ambient oxygen concentration per se has resulted in improved incubator design. Newer models provide an ambient oxygen concentration of less than 40 per cent at a flow rate of 3 l/min., but can be adjusted to supply 60-70 per cent oxygen when necessary (Table 49). This is of particular importance in the treatment of infants with venous-arterial shunts, as shunted blood does not perfuse the lung alveoli. Even so, the addition of oxygen to the blood which does undergo gas exchange in the lung may improve tissue oxygenation. The danger of pulmonary epithelial damage - the Lorrain-Smith (1899) effect - from the inhalation of high oxygen concentrations is probably of importance in humans (Nash et al., 1967; Northway et al., 1967; Banerjee et al., 1972), and should be borne in mind whenever high concentrations of oxygen are used therapeutically for a prolonged period.

SUMMARY

The oxygen concentrations attained in tents and incubators during routine paediatric use are reported. An oxygen concentration of 50-60 per cent is most readily attained in the Oxygenaire Humidaire Tent - the most efficient of the tents tested. Accurately controlled oxygen therapy in the range of 24-34 per cent is attainable in the Venturi Head Tent, which may find a place in paediatric oxygen therapy. Incubators in neonatal use generally fulfil their manufacturers' specifications. The oxygen concentrations in tents and incubators should be measured frequently during use and regulated so as to maintain the arterial Po_2 at or near an optimal level.

IMPLICATIONS FOR THE FUTURE

IMPLICATIONS FOR THE FUTURE

The observations presented in this thesis have important implications both for service and future research. They confirm that hypoxaemia and acid-base abnormalities occur frequently in children with acute respiratory illnesses, and that it may not be possible to assess their degree clinically. Objective measurements of arterial blood gas tensions and pH are invaluable in guiding treatment in many patients, and facilities for these methods are increasingly available in hospital. The special problems in the care of the children with severe respiratory failure reported here support the contention (Jones, 1966) that properly staffed, well equipped units, with adequate laboratory support are necessary for the optimal management of such cases.

The early detection and treatment of functional abnormalities in children with chronic conditions, such as asthma and cystic fibrosis, may reduce the number who might otherwise develop episodic respiratory insufficiency. Pulmonary function studies, mainly on an out-patient basis, make a large contribution to diagnosis and management in such cases, (Polgar and Promadhat, 1971). Ideally, therefore, the provision of facilities for pulmonary function testing should complement the development of the special in-patient units described.

The observations presented have been concerned largely with the diagnosis and treatment of hypoxaemia in respiratory disorders in children. The scope for future research is much wider. More information is also needed about the aetiology, prognosis and possible prevention of the conditions studied.

Further studies of pulmonary function in acute respiratory infections in infants might profitably be combined with detailed

aetiological investigations. Recent reports from Australia (Rooney and Williams, 1971) suggest an association between respiratory syncitial virus (R.S.V.) infections in infancy and the development of asthma later. A carefully controlled longitudenal study, including serial testing of pulmonary function is required to define the natural history of these disorders and their possible relationship to childhood asthma, and obstructive airway disease in adult life.

The limitations of measurements of blood lactate and pyruvate concentrations in the diagnosis of tissue hypoxia have been discussed. Recent studies suggest that the lactate/pyruvate ratio in cerebro-spinal fluid reflects changes in the cerebral NADH/NAD^+ system, both in experimental hypoxia (Siesjö et al., 1968; Kaasik et al., 1970) and in clinical cases in which cerebral hypoxia is presumed to be present (Ponten et al., 1968; Svenningsen and Siesjö, 1972). Further studies in acutely hypoxaemic infants (in many of whom cerebro-spinal fluid is sampled to exclude meningitis), should help clarify the immediate and prognostic importance of these indices.

There is scope for reassessing and perhaps improving existing methods of management of patients with acute and chronic respiratory failure. The use of controlled oxygen therapy in cystic fibrosis and asthma should be thoroughly evaluated, and methods, acceptable to ill children, devised for the administration of oxygen at a concentration of 28-30 per cent. It may also be appropriate to assess the chemo-receptor responses of normal infants and children, in view of the readiness with which carbon dioxide retention occurs during acute respiratory illnesses.

The limits of safety of buffers at present used in the treatment of acute respiratory failure merits further study, including direct measurement of the osmolar changes which occur during their administration. There is also a need to rationalise methods for providing ventilatory support to patients with severe ventilatory insufficiency. The determination of the lung volume during spontaneous or assisted ventilation at which optimal gas exchange occurs with minimal utilisation of alveolar surface active material, has aroused the interest of investigators dealing with adults and newborn infants (Ashbaugh et al., 1969; McIntyre, 1969; Kumar et al., 1970; Gregory et al., 1971). The therapeutic approaches suggested by these studies should be evaluated in infants and children with respiratory insufficiency.

The possible prevention of acute respiratory illnesses in infancy caused by R.S.V. is the most promising area of prophylaxis. Recent evidence, Chanock et al., 1970, that an immunological reaction involving serum antibodies is important in the pathenogenesis of disease produced by this virus, suggest that methods should be developed which are effective in stimulating local respiratory tract secretory antibody. Further elucidation of the immunological aspects of R.S. diseases may well be followed by the development of an effective risk-free vaccine.

APPENDIX

APPENDIX 1

Use of Siggaard Andersen's Nomogram In Vivo

Base excess of blood changes *in vivo* with Pco_2 changes due to HCO_3^- ion movements between blood and tissue extracellular fluid. ECF, devoid of haemoglobin, is unbuffered against Co_2, and effectively dilutes the blood haemoglobin's buffering ability. The relationship between base excess and Pco_2 *in vivo* can be predicted using the nomogram as follows:

1 Measure arterial pH, Pco_2 and haemoglobin of the subject.

2 Draw a line through pH and Pco_2 on the nomogram.

3 Use as fulcrum the intersection of this line with the base excess grid haemoglobin line equal to one third of the subject's actual haemoglobin.

4 Connect this fulcrum to $Pco_2 = 40$.

5 Read base excess where the new line crosses the actual haemoglobin concentration. This line also predicts the pH and plasma HCO_3^- at $Pco_2 = 40$.

- oOo -

APPENDIX 2

Deaths from Pneumonia and Bronchiolitis (see Section II, Chapter 1)

Case 30

This eight-week old infant had been born at home after a normal pregnancy and delivery at term (birth weight 2.7 Kg). She was admitted to hospital with a three day history of cough, nasal discharge and progressive respiratory distress.

On examination, she was febrile, dehydrated, pale and shocked. Respirations were rapid and deep, and associated with intercostal indrawing and diminished breath sounds bilaterally. Occasional basal crepitations were heard. No cardiac or neurological signs were noted. Chest X-ray revealed extensive pneumonia bilaterally (Plate XII).

She was treated with antibiotics, intravenous fluid and electrolytes, and hydrocortisone. She was nursed in 50-70 per cent oxygen. There was some immediate improvement, but three hours later she developed cyanosis and generalised mottling of the skin. Respirations became irregular and widespread crepitations were audible throughout both lung fields. Pulmonary oedema was suspected. Arterial pH was 7.14 and Pco_2 54 mm Hg. She was treated with sodium bicarbonate, intubated and ventilated with a Bird ventilator. Progressive circulatory failure supervened and she died some hours later.

At autopsy there were extensive bronchopneumonic changes throughout both lung fields. No congenital abnormalities were detected. No bacterial pathogens were isolated from cultures of blood or lung aspirate after death.

Extensive pneumonia accompanied by shock, dehydration, hypernatraemia and severe acidosis were the main factors contributing to a fatal outcome.

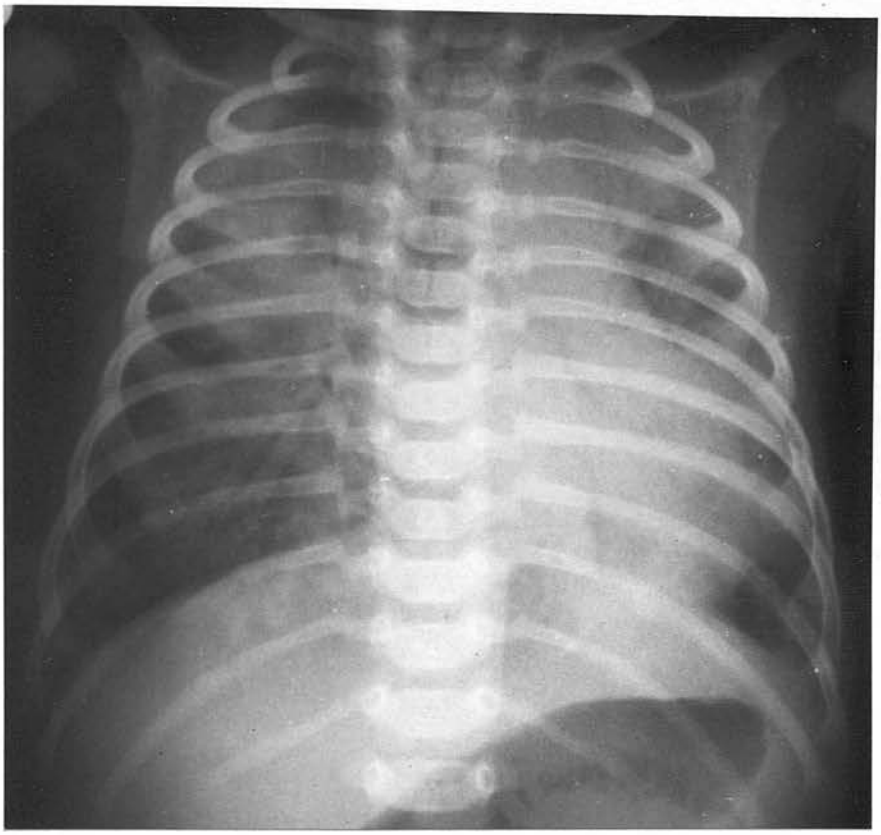

Plate XII

Chest X-ray appearance during terminal illness (Case 30).

Case 36

This three-month old infant was admitted to hospital at the request of his parents who were concerned about the deterioration in his condition after two days of increasing respiratory distress, pallor and difficulties in feeding. A lumbo-sacral meningomyelocoele had been repaired soon after birth and a Pudenz valve had been inserted because of progressive hydrocephalus.

On admission he was pale and febrile with rapid grunting respirations. Scatter rhonchi and crepitations were audible throughout both lung fields. Liver and spleen impalpable. There was no evidence of raised intracranial pressure or meningeal irritation. The back was well healed. A clinical diagnosis of pneumonia was made and confirmed radiologically (Plate XIII).

Within a few hours of his admission, his condition deteriorated further and he was cyanosed with marked respiratory distress, abdominal distension and peripheral oedema. He was treated intensively with oxygen, antibiotics, digoxin, frusemide and hydrocortisone. His anaemia was partially corrected with a cautious blood transfusion. His condition deteriorated relentlessly, however, and he died two days later.

At autopsy the main finding was that the cardiac catheter of the Pudenz valve system was situated in relation to the tricuspid valve, which had a large vegetation on the lateral cusp, emboli from which had caused multiple pulmonary infarcts associated with bronchopneumonic changes. The hydrocephalus which was due to a small Chiari malformation was well controlled by the shunt and there was no evidence of meningitis or ventriculitis.

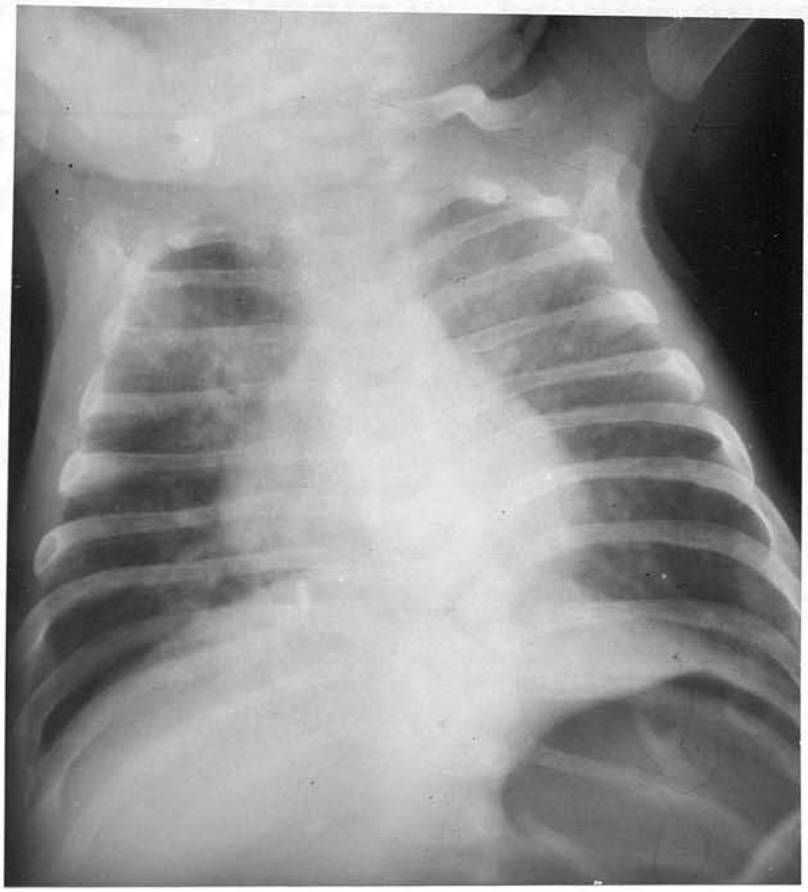

Plate XIII

Chest X-ray appearance during terminal illness (Case 36)

Case 42

This seven-month old infant had been born in hospital at term (birth weight 3.7 Kg). He was admitted to hospital with a history of cough and increasing respiratory distress of several weeks duration. There had been little response to repeated courses of antibiotics.

On examination he was some two standard deviations below expected weight, and was cyanosed breathing air. Respiratory distress was marked and crepitations were audible at both lung bases. No cardiac murmurs were heard and there were no signs of cardiac failure initially. The spleen was not palpable. The chest X-ray confirmed the diagnosis of pneumonia, predominantly affecting the left upper lobe (Plate XIV). No organisms were grown from nasal and throat swabs or blood culture. No virus antibodies were detected in a single blood sample. Plasma protein electrophoresis showed a deficiency of gammaglobulin. Gamma G globulin was 32 mgm per 100 ml, gamma m globulin 12 per cent of standard reference serum and gamma A globulin was not detectable.

Despite treatment with humidified oxygen, antibiotics and gamma-globulin (given in anticipation of the diagnosis) his condition steadily deteriorated and he died several days later. At autopsy the lungs showed widespread bronchopneumonic changes. The thymus was completely atrophic. No lymph nodes were found. Malpighian corpuscles were not identified in the spleen.

Case 44

This three-week old baby had been born in hospital at term following an induced delivery because of maternal hypertension. She weighed 3.6 Kg at birth. She remained well until five days before admission when she developed loose offensive stools and an irritating

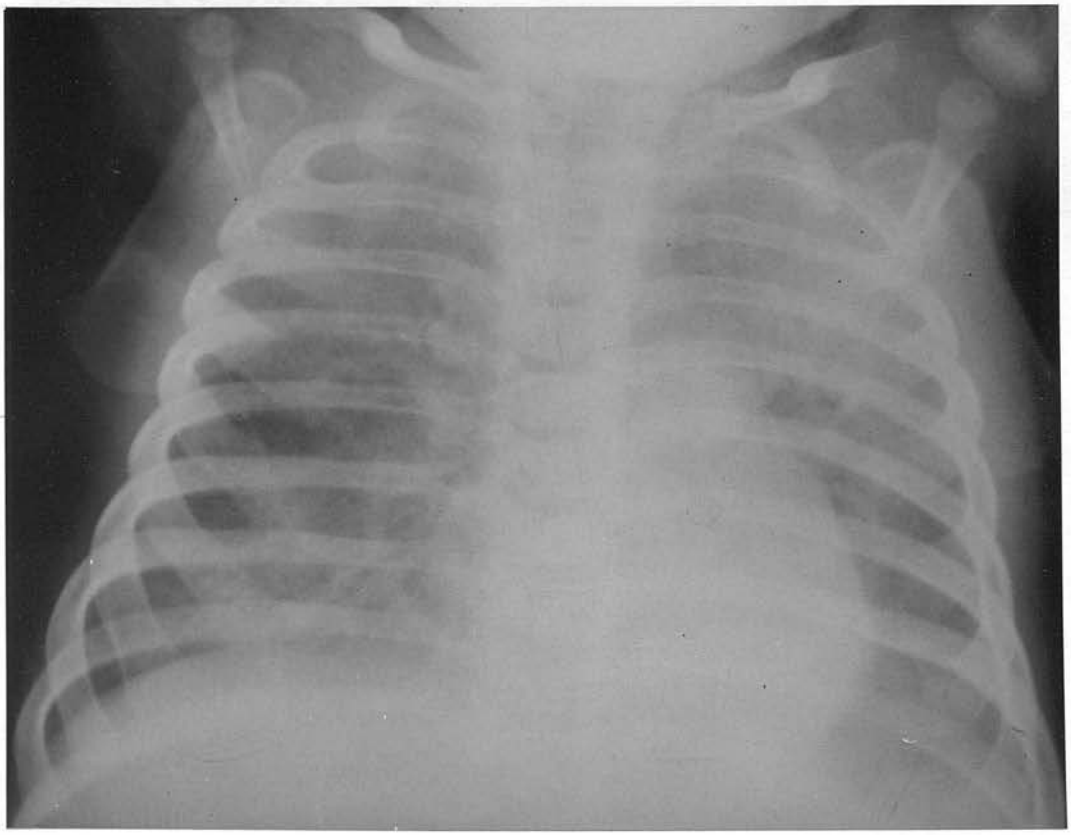

Plate XIV

Chest X-ray appearance during terminal illness (Case 42)

cough. Three days later she was seen by the family doctor who diagnosed an upper respiratory tract infection and started treatment with antibiotics. The following day she was referred to hospital because of increasing respiratory distress, pallor and refusal of feeds. Two siblings had recently had diarrhoea. The family history was otherwise unremarkable.

On examination, she was cyanosed in air and moderately dehydrated. She was markedly dyspnoeic and widespread crepitations were audible throughout both lung fields. There were no cardiac murmurs and no signs of cardiac failure. The spleen was impalpable. Fontanelle tension was normal and there was no neck retraction. A diagnosis of pneumonia was made clinically and confirmed radiologically (Plate XV). She was treated with 40-50 per cent humidified oxygen and antibiotics, and intravenous fluids.

At first, she appeared to improve and was pink in oxygen. After four hours she became cyanosed and apnoeic, following a bout of coughing. The trachea was intubated and copious, frothy, blood-stained secretions were aspirated. The tube remained in situ to facilitate aspiration of secretions. Some hours later congestive cardiac failure was diagnosed, and digoxin and diuretics were prescribed. Again she improved clinically but within a few hours developed recurrent generalised convulsions. Despite anticonvulsants and mechanical assistance to ventilation, she died soon after.

At autopsy extensive bronchopneumonia was present but no congenital defect was noted. Shig. sonnei were isolated from a rectal swab. No bacterial pathogens were isolated from throat or nasal swabs, blood culture or lung aspirate after death.

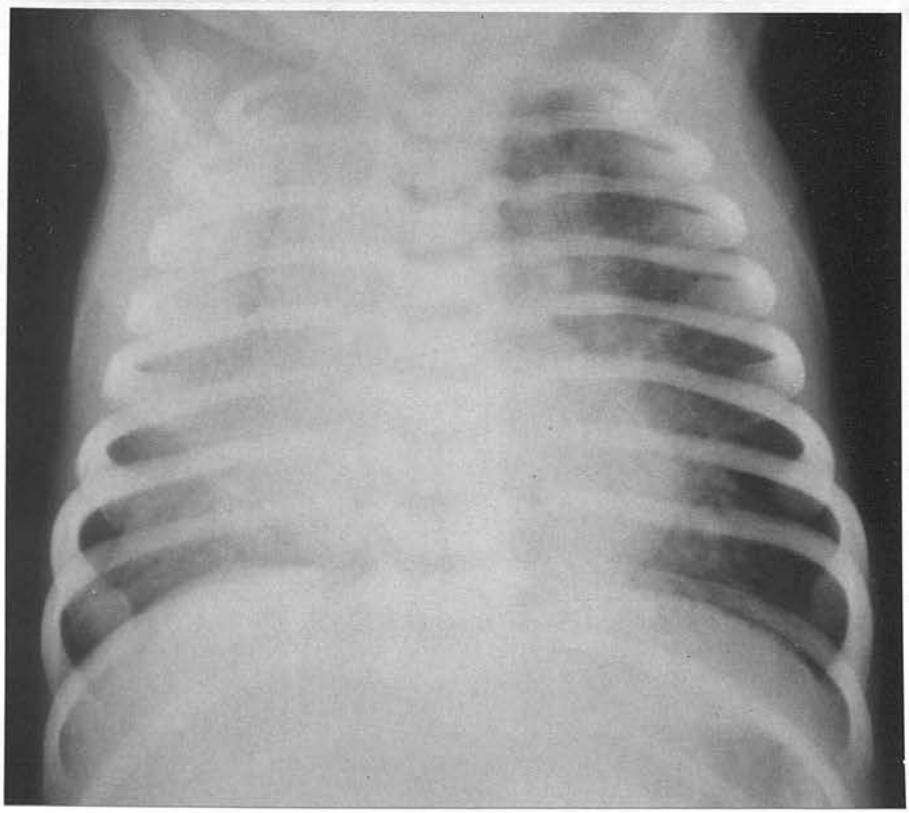

Plate XV

Chest X-ray appearance during terminal illness (Case 44)

Severe pneumonia with repeated accumulation of secretions in the airways, cardiac failure and uncontrolled convulsions contributed to a fatal outcome in this case. A reappraisal of intravenous fluid therapy confirmed that only 200 ml fluid had been administered over a 15 hour period, suggesting that overhydration was an unlikely explanation for the observed sequence of events.

Case 45

This four-week old baby had been born in hospital at term (birth weight 3.8 Kg) after a normal pregnancy and delivery. She had progressed normally until the day of admission to hospital when she refused feeds and developed grunting respirations. Mother had noted blood-stained secretions on the pillow following bouts of coughing. No other family member was affected.

On examination, she was pale, cold, dehydrated and shocked. Respirations were grunting in character and crepitations were audible throughout both lung fields. There were no cardiac murmurs or signs of cardiac failure. The spleen was not enlarged. No neurological signs were noted. X-ray of the chest confirmed the clinical diagnosis of widespread bronchopneumonia. She was nursed in humidified oxygen (60-80 per cent) and treated with intravenous ampicillin and cloxicillin. Sodium bicarbonate was infused to correct metabolic acidosis. Four hours later she deteriorated suddenly and became cyanosed and then apneoic. Attempts at resuscitation with endotracheal intubation, suction and cardiac massage were not successful and she died within a few minutes.

At autopsy widespread pneumonic changes were present in both lungs. No congenital abnormalities were noted. E coli 0127 were isolated from a rectal swab. No organisms were isolated from cultures from the nose,

throat, blood and lung aspirate after death. Virology studies were not undertaken.

Shock, anaemia, hypothermia and dehydration may all have contributed to the fatal outcome in this patient. The sudden deterioration terminally was thought to have been caused by accumulation of secretions in the airways.

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TABLES

TABLE 1

NUMBER OF ADMISSIONS*, DEATHS AND AGE AT DEATH OF 550 INFANTS AND CHILDREN DURING THE YEARS 1957-66 (INCLUSIVE)

Year	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	TOTAL	
No of ADMISSIONS	1680	1663	1733	1680	1686	1771	1918	2002	2162	2309	18,604	
No of DEATHS	72	45	65	61	53	50	60	44	47	53	550	
Age at Death												
Birth - 1 month	23	13	23	17	13	18	23	20	17	22	189	(34%)
1 month - 1 year	27	19	21	24	20	17	16	14	15	17	190	(35%)
1 year onwards	22	13	21	20	20	15	21	10	15	14	171	(31%)

The proportion of patients with acute lower respiratory infection (as a percentage of the total number of admissions) was calculated for the years 1958, 1962, 1967 and found to be 12.6, 13.1 and 13.8 per cent respectively.

TABLE 1a

NUMBER OF DEATHS ACCORDING TO QUARTER OF YEAR IN WHICH THEY OCCURRED

Year	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	TOTAL	
No of DEATHS	72	45	65	61	53	50	60	44	47	53	550	
Time of Occurrence												
January-March	16	17	26	16	15	18	16	11	20	15	170	(31%)
April-June	18	12	18	16	12	12	17	10	7	12	134	(24%)
July-September	15	8	13	10	12	8	11	12	10	10	109	(20%)
October-December	23	8	8	19	14	12	16	11	10	16	137	(25%)

TABLE 1b

TOTAL DEATHS, CARDIAC AND PNEUMONIA DEATHS OCCURRING EACH YEAR (1957-66)

Year	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	TOTAL	
Total No of DEATHS	72	45	65	61	53	50	60	44	47	53	550	
Cardiac Deaths	10	11	18	10	10	12	13	6	9	18	117	(21%)
Pneumonia Deaths	15	6	15	8	4	10	5	5	9	9	86	(16%)

TABLE 2

MAIN CAUSES OF DEATH - 550 INFANTS AND CHILDREN (RHSC ED. 1957-66)

			Total No	%
1	CONGENITAL DISORDERS		176	(32)
	Congenital Heart Disease	117		
2	RESPIRATORY TRACT DISORDERS		120	(22)
	Pneumonia	86		
3	INFECTIONS (excludes those in 1, 2 and 5)		46	(8)
	Septicaemia	29		
	Meningitis	17		
4	MALIGNANCY		46	(8)
	Leukaemia	34		
5	NEUROLOGICAL DISORDERS (excludes those in 1, 3, and 4)		37	(7)
	Encephalitis, Convulsions, Encephalopathy	20		
	Cerebral Birth Trauma	8		
6	HYPOTHERMIA		24	(4)
7	HAEMATOLOGICAL DISORDERS (excluding those in 4)		22	(4)
	Haemorrhagic Diathesis	10		
	Aplastic and Haemolytic Anaemia	8		
8	MISCELLANEOUS		63	(11)
	G.I. and Hepatobiliary	15		
	Renal	12		
	"Prematurity"	9		
	Poisoning	6		
9	UNCLASSIFIED		16	(3)
		TOTAL:	550	

TABLE 2a

NEONATAL DEATHS (0 - 1/12)

(According to Ward Coding Index)

			Total No
1	CONGENITALLY DETERMINED DISORDERS		75
	Congenital Heart Disease	52	
2	RESPIRATORY DISORDERS		37
	Pneumonia	19	
	Respiratory Distress or Failure	18	
3	INFECTIONS (excluding those in 2)		19
	Septicaemia	10	
	Meningitis	9	
4	HYPOTHERMIA		17
5	NEUROLOGICAL DISORDERS		8
	Cerebral Birth Injury/Anoxia	8	
6	HAEMATOLOGICAL DISORDERS		8
	Haemorrhagic Disease	5	
	Rh. Isoimmunisation	3	
7	MALIGNANCY		2
8	MISCELLANEOUS		15
	"Prematurity"	9	
9	UNCLASSIFIED		8
		TOTAL:	189

TABLE 2b

DEATHS (1/12 - 1 YEAR)

(According to Ward Coding Index)

			Total No
1	CONGENITALLY DETERMINED DISORDERS		79
	Congenital Heart Disease	54	
2	RESPIRATORY TRACT DISORDERS		51
	Pneumonia	46	
3	INFECTIONS (excluding those in 2)		15
	Septicaemia	13	
	Meningitis	2	
4	HAEMATOLOGICAL DISORDERS (excluding Leukaemia)		9
5	HYPOTHERMIA		7
6	NEUROLOGICAL DISORDERS (excluding those in 1)		7
7	MALIGNANCY		2
	Leukaemia	2	
8	MISCELLANEOUS		18
9	UNCLASSIFIED		2
		TOTAL:	190

TABLE 2c

DEATHS (1 - 12 YEARS)

(According to Ward Coding Index)

			Total No
1	MALIGNANCY		42
	Leukaemia	32	
2	RESPIRATORY TRACT DISORDERS		32
	Pneumonia	21	
3	CONGENITALLY DETERMINED DISORDERS		22
	Congenital Heart Disease	11	
4	NEUROLOGICAL DISORDERS (excluding those in 1 and 3)		22
	Encephalitis, Convulsions, Encephalopathy	15	
5	INFECTIONS (excluding those in 2 and 4)		12
	Meningitis	6	
	Septicaemia	6	
6	HAEMATOLOGICAL (excluding those in 1)		5
7	HYPOTHERMIA		0
8	MISCELLANEOUS		30
	Renal	10	
	Poisoning	6	
9	UNCLASSIFIED		6
		TOTAL:	171

TABLE 3

DEATHS FROM RESPIRATORY DISEASES

			Total No
1	ACUTE RESPIRATORY TRACT INFECTIONS		98
	Pneumonia	86	
	Laryngo-tracheo-bronchitis	12	
2	RESPIRATORY DISTRESS SYNDROME or RESPIRATORY FAILURE IN NEWBORNS		18
* 3	CYSTIC FIBROSIS OF PANCREAS		15
4	ASTHMA		1
5	DROWNING		1
6	PULMONARY FIBROSIS		1
7	BRONCHIECTASIS		1
	TOTAL:		135 +

* NB Included under Congenitally Determined Disorders in Table 2.

+ 24.5% of total deaths.

TABLE 4

BASIS OF DETAILED ANALYSIS OF DEATHS

(Adapted from Table 2)

	No of Cases	No of records available
1 CONGENITALLY DETERMINED DISORDERS		
Congenital Heart Disease	117	72
Cystic Fibrosis of Pancreas	15	10
2 RESPIRATORY TRACT DISORDERS		
Pneumonia	86	50
Laryngo-tracheo-bronchitis	12	8
3 INFECTIONS		
Septicaemia	29	14
6 HYPOTHERMIA	24	15
8 MISCELLANEOUS		
"Prematurity"	9	4

TABLE 5

ANALYSIS OF CASE RECORDS OF 72 INFANTS DYING OF CONGENITAL HEART DISEASE

		No of Cases
1	AGE	
	0 - 6 days	14
	1 week - 1 month	9
	1 month - 1 year	42
	1 - 5 years	7
2	SEX	
	Male	39
	Female	33
3	DURATION IN HOSPITAL	
	1 day	30
	1 - 3 days	10
	3+ days	32
4	AUTOPSY	
	Yes	62
	No	10
5	POST-MORTEM DIAGNOSIS (62 cases)	
	Transposition of great vessels	12
	Fallot's tetralogy	8
	Ventricular Septal Defect	6
	Patent ductus arteriosus	5
	Tricuspid atresia	4
	Endocardial cushion defects	4
	Coarctation of aorta	3
	Left heart syndrome	3
	Endocardial fibroelastosis	3
	Pulmonary stenosis	2
	Truncus arteriosus	2
	Total anomalous pulmonary venous drainage	1
	Myocarditis	1
	Miscellaneous (complex lesions)	8
6	PREVIOUS INVESTIGATION	5
7	PREVIOUS OPERATION	2
8	ASSOCIATED CONGENITAL ABNORMALITIES	
	Mongolism	6
	Multiple defects	6
	Neurological	3
	Miscellaneous	2
9	ASSOCIATED PNEUMONIA AND ATELECTASIS	25

TABLE 6

ANALYSIS OF CASE RECORDS OF 44 INFANTS WHO DIED OF BRONCHOPNEUMONIA

		NUMBER OF CASES		
		Associated Defect	No Associated Defect	Total
1	AGE AT ONSET			
	0 - 7 days	2	3	5
	7 - 28 days	0	9	9
	1 month - 1 year	5	13	18
	1 - 12 years	12	0	12
2	SEX			
	Male	12	14	26
	Female	7	11	18
* 3	DURATION IN HOSPITAL PRIOR TO DEATH			
	1 day	9	12	21
	1 - 3 days	5	9	14
	> 3 days	5	4	9
4	AUTOPSY			
	Yes	15	17	32
	No	4	8	12
5	PROBABLE CONTRIBUTORY CAUSE			
	Hypothermia	0	10	10
6	ASSOCIATED ABNORMALITIES			
	Neurological Defects			9
	Congenital heart disease			3
	Down's Syndrome			3
	Miscellaneous			5

* The average duration of illness (prior to admission) of infants dying a) within one day, and b) after one day of admission to hospital, was three days and four days respectively.

TABLE 7

DESCRIPTION OF PATIENTS

Case Number	Sex	Age (Months)	B.Wt. (Kg.)	Wt. (Kg.)	Previous‡ Respiratory Illness	History (days)	Prior* Antibiotics	Clinical Diagnosis
1	F	1	3.0	3.0	+	4	-	Bronchiolitis
2	F	7	2.7	5.8	-	4	-	"
3	F	2	2.8	3.7	-	4	+ (P)	"
4	M	1	2.9	4.3	-	3	+ (T)	"
5	F	2	2.5	3.8	-	3	-	"
6	F	2	4.0	5.8	-	7	+ (P)	"
7	M	13	2.7	9.8	+	3	+ (P)	"
8	M	2	2.5	4.5	-	4	+ (T)	"
9	M	1	2.8	3.8	-	6	+ (P)	"
10	F	10	3.0	8.1	+	1	-	"
11	F	2	3.7	4.7	-	10	+ (P)	"
12	M	17	0.9	8.7	+	2	-	"
13	M	4	3.5	6.8	-	2	-	"
14	M	0.5	2.1	2.0	-	7	+ (A,C)	"
15	F	2	2.4	5.3	-	1	-	"
16	M	1	2.7	3.1	-	4	-	"
17	M	5	3.5	5.3	-	5	+ (P)	"
18	M	3	3.6	4.8	-	10	+ (P)	"
19	M	6	1.5	6.8	-	3	+ (A)	"
20	F	7	3.5	5.8	+	-	+ (A,C)	"
21	F	19	2.1	10.5	-	7	+ (P)	Pneumonia
22	M	2	3.2	4.3	+	7	+ (P)	"
23	M	2	3.4	3.7	-	1	-	"
24	F	6	3.0	8.6	-	7	-	"
25	M	1	2.0	2.5	-	1	-	"
26	F	9	3.5	12.1	-	5	-	"
27	M	8	3.6	9.0	+	2	-	"
28	F	2	1.8	2.3	-	3	-	"
29	M	35	3.6	14.4	+	4	+ (P)	"
30	F	2	2.6	-	-	3	-	"
31	M	7	3.3	6.8	+	3	-	"
32	M	1	3.9	4.5	-	1	-	"
33	M	10	3.0	-	+	2	-	"
34	F	4	2.8	4.4	-	3	-	"
35	F	5	1.8	6.3	+	3	+ (E)	"
36	M	3	3.3	3.9	-	2	-	"
37	M	<1	3.4	-	-	1	-	"
38	M	9	3.1	8.3	+	5	+ (P)	"
39	F	18	2.7	6.3	+	2	-	"
40	F	7	2.8	5.3	-	1	-	"
41	F	5	3.1	5.8	+	-	-	"
42	M	7	3.9	6.8	+	-	+ (?)	"
43	M	1	3.0	3.0	-	1	-	"
44	F	<1	3.6	3.3	-	4	+ (P)	"
45	F	1	3.9	4.5	-	1	-	"

‡ Bronchitis
Bronchiolitis
Croup

* P: Penicillin
T: Tetracycline
A: Ampicillin
C: Cloxacillin
E: Erythromycin

TABLE 11a

MEASUREMENTS AT TIME OF ADMISSION TO SERIES IN 27 INFANTS BREATHING AIR

	Po_2 mm Hg	Pco_2 mm Hg	pH	So_2 %	$A\text{-}aDo_2$ mm Hg	BE mEq/l
Np	20	27	27	20	20	27
Mean	62	44	7.36	85.2	35	+ 1.3
± S.D.	18	13	0.07	13.4	17	5.0
Range	29 - 91	24 - 75	7.23	44.8	11	-13.4
			- 7.49	- 96.7	- 67	- + 6.8

TABLE 11b

BLOOD GAS TENSIONS AND pH IN DIFFERENT RADIOLOGICAL GROUPS

Radiological Grade		Po_2 +	Pco_2	pH	$A\text{-}aDo_2$ + mm Hg
SP	Mean	65.1	44.4	7.34	30.6
Np = 16	S.D.	17.4	10.9	0.05	15.7
	Ns	9	16	16	9
LP	Mean	64.7	47.3	7.35	26.0
Np = 8	S.D.	15.5	12.1	0.09	10.8
	Ns	3	8	8	3
BP	Mean	56.5	48.7	7.34	42.1
Np = 20	S.D.	19.5	14.4	0.10	17.8
	Ns	8	20	20	8

\+ measured breathing air

Np - Number of patients
Ns - Number of samples

The differences between groups are not statistically significant. ($P > 0.10$ for each possible comparison).

TABLE 11a

MEASUREMENTS AT TIME OF ADMISSION TO SERIES IN 27 INFANTS BREATHING AIR

	Po_2 mm Hg	Pco_2 mm Hg	pH	So_2%	A-aDo_2 mm Hg	BE mEq/l
Np	20	27	27	20	20	27
Mean	62	44	7.36	85.2	35	+ 1.3
± S.D.	18	13	0.07	13.4	17	5.0
Range	29 - 91	24 - 75	7.23	44.8	11	-13.4
			- 7.49	- 96.7	- 67	- + 6.8

TABLE 11b

BLOOD GAS TENSIONS AND pH IN DIFFERENT RADIOLOGICAL GROUPS

Radiological Grade		Po_2 +	Pco_2	pH	A-aDo_2 + mm Hg
SP	Mean	65.1	44.4	7.34	30.6
Np = 16	S.D.	17.4	10.9	0.05	15.7
	Ns	9	16	16	9
LP	Mean	64.7	47.3	7.35	26.0
Np = 8	S.D.	15.5	12.1	0.09	10.8
	Ns	3	8	8	3
BP	Mean	56.5	48.7	7.34	42.1
Np = 20	S.D.	19.5	14.4	0.10	17.8
	Ns	8	20	20	8

\+ measured breathing air

Np - Number of patients
Ns - Number of samples

The differences between groups are not statistically significant. ($P > 0.10$ for each possible comparison).

TABLE 12

EFFECT OF 40% - 45% OXYGEN IN 16 PATIENTS ON ADMISSION OR WITHIN 48 HOURS

Case Number	‡‡FIo_2 %	Po_2 mm Hg	Pco_2 mm Hg	pH	X-ray Diagnosis
2	32*	43	66	7.26	BP + O1
	43*	76	66	7.30	
13	21	60	45	7.38	SP + O1
	42	141	50	7.38	
16	40	112	59	7.44≠	LP + O1
18	40	145	51	7.45	BP + O1
19	40	175	39	7.28	SP + O1
21	21	45	29	7.44	BP + O1
	45*	59	34	7.45	
22	29*	52	64	7.25	SP
	45*	74	64	7.26	
25	21	49	57	7.33	BP + O1
	45*	137	50	7.34	
31	40	96	33	7.38	SP
33	21	43	50	7.28	SP + O1
	45	140	46	7.29	
36	21	47	32	7.39	SP + O1
	40	83	31	7.39	
37	45	220	28	7.17	LP
38	21	65	41	7.42	LP
	40	115	39	7.45	
43	40	94	64	7.29	LP
44	40	112	37	7.37	LP
45	40	45	46	7.21	BP
	100	108	49	7.21	

‡‡ In cases 13, 33, 36, 38 and 45 the time interval between samples was 30-45 minutes.

* Mean of values obtained before and after arterial blood sampling.

≠ Prior infusion of sodium bicarbonate

TABLE 13

ACID-BASE CHANGES AFTER ADMISSION TO HOSPITAL

Case Number	Time (days)	Pco_2 (mm Hg)	Base Excess (mEq/l)
1	5	54	- 1.8
	7	37	+ 2.0
2	5	66	+ 1.4
	6	46	+ 6.0
3	5	75	+ 2.7
	7	53	+ 5.9
6	8	53	+ 5.1
	9	55	+ 7.0
8	5	58	- 0.3
	6	48	+ 1.0
13	3	45	+ 1.1
	4	46	+ 3.4
22	8	64	- 0.6
	9	51	+ 6.8
25	2	57	+ 3.1
	3	53	+ 8.3

* Time in days refers to the time from the start of the lower respiratory infection, the first value being that obtained on admission.

TABLE 14

SYMPTOMS PRIOR TO ADMISSION TO HOSPITAL

Case No	Age (weeks)	Sex	Symptoms	Duration (days)	Previous Antibiotics	Outcome
1	6	M	Respiratory distress	1	Nil	Died
			Choking attacks	1		
			Cyanosis	1		
2	3	M	Cough	3	Nil	Died
			Respiratory distress	3		
			Refusal of feeds	2		
3	5	F	Cough	7	Nil	Died
			Respiratory distress	1		
			Cyanotic attacks	1		
4*	21	F	Cough	5	Ampicillin	Died
			Wheeze	4		
			Refusal of feeds	2		
5	24	F	Snuffles	14	Crystalline	Survived
			Fever and irritability	1	Penicillin	
			Cough	1		

* Refers to second hospital admission. Patient had been discharged from hospital ten days earlier having been treated for staphylococcal pneumonia for six weeks.

TABLE 15

CLINICAL OBSERVATIONS ON ADMISSION TO HOSPITAL

Case No	Temp °C	Respiratory Rate/min	Pulse Rate/min	Peripheral Circulatory Failure	Chest X-ray
1	31.0	Gasping	60	+	Consolidation throughout right lung; right pleural effusion
2	36.7	40	154	+	Extensive bronchopneumonia; small left pneumothorax
3	35.6	60	170	+	Consolidation and collapse of right upper lobe
4	38.1	42	140	-	Consolidation and collapse of right upper lobe
5	42.0	80	210	+	Consolidation of right upper lobe; right pleural effusion

TABLE 16

LABORATORY INVESTIGATIONS ON ADMISSION

Case No	Hb G%	WBC/cu mm	T/S	N/S	Blood Culture	Na	K	Cl	BUN mg %
						mEq/litre			
1	10.0	34,000 (N31, L61)	Staph. pyogenes	Staph. pyogenes Coliforms	Staph. pyogenes	136	4.7	92	21.0
2	15.3	13,800 (N44, L34)	Staph. pyogenes	Staph. pyogenes	Staph. pyogenes	-	-	-	18.7
3	12.0	21,600 (N64, L34)	Staph. pyogenes	Staph. pyogenes	Staph. pyogenes	142	5.8	100	8.2
4	9.4	12,200 (N41, L47)	No growth *	No growth	No growth *	-	-	-	-
5	10.8	13,700 (N86, L13)	No growth	-	No growth	134	5.3	104	22.5

* Staph. Aureus isolated from throat swab and blood culture during previous admission.

TABLE 17

INITIAL BLOOD GAS AND pH MEASUREMENTS

Case No	Time of Measurements From Admission (days)	FIo_2 %	Po_2 mm Hg	Pco_2 mm Hg	pH	So_2 %	$A\text{-}aDo_2$ mm Hg	Base Excess * mEq/litre
1	1	50-65	-	85	7.23	-	-	+ 7.5
2	1	45-65	41	76	7.23	-	-	+ 3.2
3	1	54	104	74	7.29	97.1	189	+ 8.2
4	6	45	73	90	7.14	86.5	136	+ 1.6
5	2	40	147	40	7.24	98.1	89	-10.4

* $NaHCO_3$ had not been infused previously

TABLE 18

CASE 2 - STAPHYLOCOCCAL PNEUMONIA

Date	Time	FIo_2 %	Po_2 mm Hg	Pco_2 mm Hg	pH	Base Excess mEq/litre	Clinical Comments
17/1	15.00	45-65	41	76	7.23	+ 3.2	Respirations 56/minute, pulse 170/minute, bluish-grey, moderate indrawing. Bilateral crepitations +++, rhonchi +.
	22.00	50-70	48	75	7.23	+ 3.0	Remains drowsy and flaccid, pale but not cyanosed.
18/1	09.00	60-70	53	75	7.24	+ 4.0	Respirations 72/minute, pulse 174/minute. Bilateral crepitations ++, rhonchi ++.
	18.00	40-70	58	56	7.35	+ 5.0	Active and alert. Moderate respiratory distress.
19/1	02.00	50-70	45	100	7.13	+ 3.5	Sudden deterioration due to accumulation of secretions. Intubated, secretions aspirated. Controlled ventilation with Bird respirator. Some $NaHCO_3$ infused.
	04.00	97	65	98	7.13	+ 2.8	Developed bilateral pneumothorax and extensive collapse both lungs.
	07.00						Died

TABLE 19

CASE 5 - STAPHYLOCOCCAL PNEUMONIA

Date	FIo_2 %	Po_2 mm Hg	Pco_2 mm Hg	pH	Base Excess mEq/litre	Clinical Comments
6/6	-	-	-	-	-	Admitted. Respirations 80/minute, pulse 210/minute, pale, marked indrawing. Right-side crepitations +++. Temperature 42°C.
7/6	40	147	40	7.24	- 10.4	Pink in O_2. Respirations 64/minute, pulse 150/minute. Temperature 38.7°C. $NaHCO_3$ infusion to correct metabolic acidosis.
8/6	41	110	43	7.37	- 0.2	Moderate respiratory distress persists. Temperature 38°C.
12/6	21	46	60	7.33	+ 5.2	15 ml purulent material aspirated from right pleural cavity (preceded measurements). Slightly cyanosed in air.
16/6	21	48	48	7.37	+ 2.5	Respirations 50/minute, pulse 150/minute. Temperature 39°C. Slight cyanosis. Increased air entry to right lung.
22/6	21	60	38	7.38	- 2.2	Alert. Clinical improvement maintained. Crepitations persist + on right side.
28/6	21	46 +	42	7.39	+ 0.8	Alert. Respirations 40/minute, pulse 140/minute. Temperature 37.3°C. Slightly dull right base. Occasional crepitations persist.
9/7						Discharged

+ No further measurement of Po_2 obtained

TABLE 21

ARTERIAL BLOOD GAS TENSIONS AND pH ON ADMISSION

Case Number	Measured Data				Calculated Data			
	FIo_2	Po_2 mm Hg	Pco_2 mm Hg	pH	So_2 %	P_Ao_2 mm Hg	$A\text{-}aDo_2$ mm Hg	Base Excess mEq/l
1a	35	45	78	7.16	66.5	145	100	- 0.8
1b	21	55	56	7.25	82.5	77	22	- 2.8
2a	40	89+	110+	7.05	91.4	138	49	- 0.5
2b	21	65	39	7.36	92.0	95	30	- 3.5
2c	21	60	45	7.32	88.5	92	32	- 2.9
3	50	144	58	7.31	98.5	274	130	+ 3.0
4	21	50	61	7.32	81.0	73	23	+ 5.0
5	21	42	56	7.25	68.1	76	34	- 2.8
6	21	51	58	7.31	81.5	72	21	+ 3.9
7	35	-	62	7.22	-	-	-	- 1.6
8	21	47	54	7.22	73.6	80	33	- 4.9
9	21	43	50	7.28	71.4	88	45	- 2.7
10	21	59	46	7.36	89.4	91	32	+ 0.2
11	21	61	45	7.43	91.8	89	28	+ 5.0
12	21	54	36	7.41	88.3	103	49	- 1.3
13	21	59	36	7.46	91.9	104	45	+ 2.0
14	21	73	26	7.38	94.6	103	30	-10.0
15	21	61	41	7.40	91.2	97	36	+ 0.9
16	21	67	42	7.37	92.8	91	24	- 0.9
17	21	66	40	7.39	92.9	95	28	- 0.5
18	21	69	45	7.39	93.6	95	26	+ 2.5
19	21	70	39	7.38	93.8	96	26	- 1.8
20	21	70	37	7.40	94.2	103	33	- 1.4
21	21	74	43	7.37	94.5	92	18	- 0.2

FIo_2 - Inspired oxygen concentration as percentage at the time of blood-sampling.

So_2 - Arterial oxygen saturation

P_Ao_2 - Alveolar oxygen tension

$A\text{-}aDo_2$ - Alveolar/arterial oxygen tension gradient

\+ - Previous investigations had been performed in air when the Po_2 was 30 mm Hg and the Pco_2 87 mm Hg. A pH was not obtained on that sample.

TABLE 21a

ACID-BASE VARIABLES - SEVERE ACUTE ASTHMA BREATHING AIR
(20 PATIENTS)

	Po_2 mm Hg	Pco_2 mm Hg	pH	So_2 %	$A\text{-}aDo_2$ mm Hg	B.E.+ mEq/litre
Mean	59.8	44.8	7.35	87.4	30.8	- 0.8
S.D.	9.7	8.8	0.06	8.2	8.2	3.5

+ Sodium bicarbonate had not been infused previously

TABLE 26

SERUM ELECTROLYTES BEFORE AND AFTER TREATMENT WITH SODIUM BICARBONATE

CASE NO	PRE-BICARBONATE					POST BICARBONATE + (within one hour)					(after 48 hours)				
	Na	K mEq/l	Cl	Co_2 Vols %	BUN mgm %	Na	K mEq/l	Cl	Co_2 Vols %	BUN mgm %	Na	K mEq/l	Cl	Co_2 Vols %	BUN mgm %
Case 1a	-	-	-	-	-	156	4.0	106	31	24.0	144	3.0	90	28	12.8
Case 1b	-	-	-	-	-	142	4.4	100	27	12.5	-	-	-	-	-
Case 2a	142	6.1	105	31	7.7	148	4.5	104	35	9.4	138	4.5	98	30	9.1
Case 2c	140	3.8	87	35	11.7	154	4.4	95	42	13.4	140	3.7	99	28	6.7

+ 2-6 mEq/Kg B.Wt.

TABLE 27

DETAILS OF INITIAL CLINICAL ASSESSMENT

Case No	Sex	Age (years)	Age at time of diagnosis (years)	Birthweight (kg)	Present Weight (kg)	Deviation from normal weight (SD)	Predominant Symptoms	Finger Clubbing	Chest Deformity	Clinical Grade
1	M	4.0	0.5	3.50	11.1	-2	R	+	+	I
2	M	0.2	0.1	4.48	3.2	-2	R	-	-	I
3	F	4.9	3.9	2.48	15.2	-1	A	-	-	I
4	F	6.3	2.0	2.20	15.1	-1	R	++	+	I
5	M	7.7	7.7	-	20.2	-1	R	++	+++	I
6	F	4.9	3.3	2.10	17.1	Mean	A	+	+	I
7	F	4.0	1.9	3.20	12.0	-2	A	+	-	I
8	M	5.3	5.2	3.50	16.4	-1	R	++	+	II
9	M	5.0	1.3	4.00	-	-	A	+	+	II
10	F	6.0	0.7	3.90	15.6	-1	R	+++	+++	II
11	F	0.3	0.3	4.00	3.9	-2	R	-	++	II
12	M	0.2	0.2	3.10	3.7	-2	R	-	++	II
13	F	0.5	0.3	3.10	5.2	-2	A	+	+	III
14	M	4.5	1.0	4.50	15.9	-1	R	+	++	III
15	F	0.3	0.3	2.70	3.6	-2	R	-	++	III
16	M	0.3	0.3	3.62	3.8	-2	R	-	++	III
17	F	3.6	2.6	3.91	14.9	Mean	A	+	++	III
18	F	12.0	7.5	3.60	24.9	-2	R	+++	++	III
19	F	0.2	0.2	2.51	3.1	-2	A	-	+	III
20	F	0.3	0.2	4.20	3.1	-2	A	-	-	III
21	F	0.2	0.2	3.64	4.1	-2	R	-	+	III
22	M	9.7	1.2	4.74	24.0	-1	A	+++	+++	III
23	M	9.7	2.1	2.76	25.7	-1	R	+++	+++	IV
24	F	3.9	2.0	-	-	-	R	+++	+++	IV
25	M	0.8	0.3	2.76	6.0	-2	R	+++	+++	IV

\+ Mild ++ Moderate +++ Severe

R: Respiratory A: Alimentary

TABLE 28

BASIS OF CLINICAL GRADING AT TIMES OF STUDY

Grade	Respiratory Symptoms	Auscultatory Signs	Infection	
			Sputum*	Temperature
I	None	Normal or harsh vesicular breath sounds No accompaniments	None	Normal
II	Mild-Moderate	Rhonchi and/or crepitations (usually localised)	None or mucoid	Normal
III	Moderate-Severe	Rhonchi and/or crepitations (localised or wide-spread)	Mucopurulent or purulent	Normal, or low grade fever (Temp $< 37.5^{\circ}C$) Little or no systemic upset
IV	Severe	Widespread crepitations	Purulent	Persistent fever (Temp $> 37.5^{\circ}C$) Marked systemic upset

* Assessed on each occasion following physiotherapy

TABLE 29

NUMBER OF STUDIES
at different clinical grades

Case No	CLINICAL GRADES			
	I	II	III	IV
1	1	-	-	-
2	1	-	-	-
3	2	-	-	-
4	2	-	-	-
5	1	-	-	-
6	1	1	-	-
7	1	-	-	-
8	1	1	-	-
9	-	1	-	-
10	-	2	6 (1)	-
11	-	2	3 (10)	1 (4)*
12	-	3	11	15 (3)
13	-	-	2 (2)	- (1)*
14	-	1	2	-
15	-	2 (1)	1 (1)	-
16	-	1	4 (4)	2 (1)
17	-	-	1	-
18	-	-	5 (1)	-
19	-	1	7 (2)	-
20	-	4 (3)	1 (1)	-
21	1	3	1	-
22	-	-	1	-
23	-	-	-	- (3)*
24	-	-	-	- (2)*
25	-	-	-	- (3)

() Measurements in oxygen
* Terminal illness

TABLE 30

SUMMARY OF CLINICAL COURSE OF CASE 12

Born 27/6 Admitted 26/7 Died 22/12

Month	July	August	September	October	November	December
Clinical Grade	- III	III IV	III IV	III II	II III	IV IV
Peak Temp. ^{o}C	- 37.5	37.5 37.8	37.4 37.8	37.4 37.1	37.2 37.5	39.5 41.1
Weight (kg) (mid-monthly)	3.5	3.5	3.9	4.3	4.8	4.9
Blood Gas Tensions (air)						
pH	-	7.26 - 7.32	7.30 - 7.38	7.33 - 7.41	7.36 - 7.42	7.26 - 7.38
Pco_2 mm Hg	-	60 - 77	52 - 66	42 - 51	44 - 51	50 - 75
Base Excess (mEq/litre)	-	+5.0 - +7.0	+3.0 - +10.0	+3.0 - +5.0	+1.5 - +4.0	+6.0 - +12.0
(No of Samples)		(4)	(4)	(5)	(7)	(9)

TABLE 31

MEAN VALUES, STANDARD DEVIATIONS (S.D.) AND RANGES OF ACID-BASE VARIABLES IN ARTERIAL OR ARTERIALISED CAPILLARY BLOOD IN THE VARIOUS CLINICAL GRADES, BREATHING AIR

		Po_2* mm Hg	Pco_2 mm Hg	pH	So_2 %	A-a Do_2 mm Hg	Base Excess mEq/litre	Hb G%
GRADE I (Np=9)	Mean	95.6	38.3	7.40	97.2	7.2	-1.5	12.0
	S.D.	7.4	4.1	0.03	0.40	4.3	2.9	1.0
	Range	86-105	34-46	7.34-7.43	96.6-97.9	3-14	-7.0-13.0	11.3-13.5
	Ns	6	11	11	6	6	8	8
GRADE II (Np=12)	Mean	74.9	43.1	7.39	94.6	21.4	+1.2	11.4
	S.D.	7.0	4.3	0.02	1.7	6.7	2.2	1.5
	Range	61-86	37-53	7.36-7.43	90.2-96.6	10-30	-3.0-7.0	9.0-14.0
	Ns	16	22	22	16	16	22	22
		P<0.001	0.01>P>0.002	P>0.10	0.01>P>0.002	P<0.001	0.01>P>0.002	P>0.10
GRADE III (Np=13)	Mean	65.6	46.1	7.39	91.5	26.1	+2.8	11.1
	S.D.	10.0	7.5	0.03	4.4	8.3	3.2	1.4
	Range	50-86	36-71	7.33-7.47	81.8-96.5	15-40	-4.0-11.6	7.1-14.0
	Ns	22	45	45	22	22	45	45
		0.01>P>0.002	0.10>P>0.05	P>0.10	0.01>P>0.002	0.05>P>0.02	0.05>P>0.02	P>0.10
GRADE IV (Np=4)	Mean	48.0	64.3	7.33	81.8	33.5	+7.2	10.9
	S.D.	-	7.5	0.04	-	-	2.3	1.5
	Range	47-49	48-77	7.26-7.39	81.0-82.5	27-40	+3.3-+12.0	8.0-14.0
	Ns	3	18	18	3	3	18	18
			P<0.001	P<0.001			P<0.001	P>0.10

* Arterial Blood Samples only

Np: Number of patients
Ns: Number of samples analysed
P Value: Probability estimations comparing Grades I and II, Grades II and III, and Grades III and IV.

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GROUP II

ase mber	Relation to $NaHCO_3$ Therapy	Time in Relation to Therapy (minutes)	FIo_2%	Po_2 mm Hg	Pco_2 mm Hg	pH	BE mEq/l
7	Pre-	6	80	153	31	7.27	-12.5
	Post-	11½	60	157	27	7.53	-
		26	40	134	31	7.36	- 7.6
8	Pre-	1½	21	76	40	7.28	- 8.0
	Post-	6	21	56	36	7.44	+ 0.2
		31	21	102	39	7.44	+ 2.2
9	Pre-	1	21	86	51	7.28	- 2.5
	Post-	7	21	60	51	7.31	- 0.6
		29	21	100	42	7.35	- 2.0
10	Pre-	4½	21	113	35	7.35	- 6.0
	Post-	8	21	98	41	7.46	+ 5.2
		36	21	111	39	7.44	+ 2.3
11	Pre-	2	21	62	41	7.33	- 4.0
	Post-	7	21	67	38	7.43	+ 0.8
		35	21	64	33	7.48	+ 0.8
12	Pre-	1½	21	101	34	7.28	-10.5
	Post-	4	21	74	38	7.59	+13.3
		37	21	84	33	7.49	+ 1.7

TABLE 37

ACID-BASE STATUS IN RELATION TO SODIUM BICARBONATE THERAPY

			Pre-$NaHCO_3$ (2-3 mins)	Post-$NaHCO_3$ (7-8 mins)	Post-$NaHCO_3$ (33 mins)
GROUP II (n = 6)	pH	Mean	7.30	7.46^{+}	7.43^{+}
		S.D.	0.04	0.10	0.07
		S.E.	0.02	0.04	0.03
	Pco_2	Mean	38.7	38.5	36.2
		S.D.	7.12	7.77	4.40
		S.E.	2.90	3.17	1.80
	BE	Mean	- 7.3	+ 3.2^{+}	- 0.4^{+}
		S.D.	3.80	5.38	3.85
		S.E.	1.55	2.20	1.57
GROUP III (n = 10)	pH	Mean	7.28	7.42^{+}	7.41^{+}
		S.D.	0.12	0.09	0.08
		S.E.	0.04	0.03	0.03
	Pco_2	Mean	41.8	41.6	37.9
		S.D.	12.17	13.56	9.02
		S.E.	3.85	4.28	2.85
	BE	Mean	- 7.8	+ 1.5^{++}	- 0.8^{++}
		S.D.	3.74	5.96	3.30
		S.E.	1.18	1.88	1.04
GROUPS II and III (n = 16)	pH	Mean	7.29	7.43^{++}	7.42^{++}
		S.D.	0.10	0.09	0.07
		S.E.	0.03	0.02	0.02
	Pco_2	Mean	40.6	40.4	37.3
		S.D.	10.40	16.0	7.49
		S.E.	2.60	4.00	1.87
	BE	Mean	- 7.6	+ 2.1^{++}	- 0.6^{++}
		S.D.	3.66	5.63	3.39
		S.E.	0.92	1.41	0.85

Statistical significance when compared with pre-sodium bicarbonate values

\+ $0.01 > P > 0.002$

++ $P < 0.001$

TABLE 38

CHANGES IN HAEMATOCRIT (Hct%) AND MEAN CORPUSCULAR HAEMOGLOBIN CONCENTRATION (MCHC) IN RELATION TO SODIUM BICARBONATE THERAPY

			Pre-$NaHCO_3$ (2-3 mins)	Post-$NaHCO_3$ (7-8 mins)	Post-$NaHCO_3$ (33 mins)
GROUP II	Hct% (n=6)	Mean	47.8	43.0^{+}	41.9^{+}
		S.D.	8.84	8.53	9.99
		S.E.	3.61	3.48	4.08
	MCHC% (n=4)	Mean	32.9	33.3	33.5
		S.D.	0.84	0.65	0.57
		S.E.	0.42	0.32	0.28
GROUP III	Hct% (n=9)	Mean	52.6	46.7^{++}	47.4^{++}
		S.D.	5.64	7.25	6.35
		S.E.	1.88	2.42	2.12
	MCHC% (n=7)	Mean	33.5	33.8	34.7
		S.D.	1.92	2.64	1.17
		S.E.	0.72	0.99	0.44
GROUPS II and III	Hct% (n=15)	Mean	50.7	45.2^{++}	45.2^{++}
		S.D.	7.20	7.71	8.17
		S.E.	1.86	1.99	2.11
	MCHC% (n=11)	Mean	33.3	33.6	34.2
		S.D.	1.59	2.09	1.14
		S.E.	0.48	0.63	0.34

Statistical significance when compared with pre-sodium bicarbonate values:

\+ P > 0.10 (N.S.)
++ 0.01 < P < 0.05 (N.S.)

TABLE 39

ELECTROLYTE VALUES BEFORE AND AFTER $NaHCO_3$ INFUSION (GROUPS II AND III)

Case Number	Timing of $NaHCO_3$ Infusion (minutes)	Timing of Electrolyte Samples (minutes)	Electrolyte Values Na (mEq/litre)	K (mEq/litre)	Cl (mEq/litre)	Ca mg%
9	13 - 14	6	143	4.2	113	9.3
		20	148	4.0	112	9.0
11	17 - 18½	3	131	5.1	99	-
		18	140	4.8	101	8.9
		24	134	4.7	101	10.9
12	16½- 20	9	140	4.3	-	-
		15	141	4.4	-	-
		19	145	4.2	-	-
		21½	148	4.1	-	-
		27	145	3.8	-	-
		32	145	4.1	-	-
14	7 - 8	0*	142	4.7	112	9.5
		6½	144	4.5	114	9.3
		14½	152	4.5	-	-
14	9 - 12	7	140	4.9	105	-
		18½	153	3.3	102	-
16	20½- 22½	20	145	4.6	107	9.5
		29	154	4.7	104	8.6
17	15 - 17½	13	134	4.6	102	-
		23	135	4.4	100	-
21	15½- 18½	14½	143	5.4	112	9.2
		20½	152	5.1	109	8.0
23	28½- 32	27½	147	4.2	108	-
		40½	152	4.3	108	9.4

* Cord, umbilical venous

TABLE 40

DIAGNOSIS AND PHASE OF ILLNESS AT TIME OF STUDY

Clinical Diagnosis	Total Number of Patients	Phase of Illness
Pneumonia	6	Acute (6)
Asthma	13	Acute (10)
		Recovery from Acute (2)
		Chronic wheeziness (1)
Cystic Fibrosis	7	Acute (or chronic) (4)
		Chronic wheeziness (2)
		Asymptomatic (1)
Cyanotic Congenital Heart Disease	9	No associated respiratory infection or cardiac failure (9)

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TABLE 41

TREATMENT PRIOR TO INITIAL STUDIES IN CHILDREN WITH ASTHMA

Case Number	Sex	Age (yrs)	Clinical Status	Treatment in Preceding Two Hours	
				Drugs	Oxygen
1a	F	7	Severe acute asthma	Paraldehyde 5 ml im	+
1b	F	8	Severe acute asthma	Prednisolone	-
1c	F	8	Severe acute asthma	Alupent	-
2	F	5	Severe acute asthma	Adrenaline 1/1000 SCI 0.3 ml (35 min)	-
3	M	12	Severe acute asthma	Prednisolone	+
4	M	11	Severe acute asthma	Adrenaline 1/1000 SCI 0.5 ml (1 hour)	-
5	M	12	Severe acute asthma	Prednisolone	-
6	M	7	Severe acute asthma	Ephedrine	+
7	M	9	Severe acute asthma	Adrenaline 1/1000 SCI 0.4 ml (2 hours)	-
8	M	8	Severe acute asthma	Aminophylline 75 mg IV	Not known
9	M	5	Severe acute asthma	-	-
10	M	7	Chronic wheeziness	-	-
11	F	6	Recovery phase of acute asthma	-	+
12a	F	2	Recovery phase of acute asthma	-	+

TABLE 42

INITIAL MEASUREMENTS IN INFANTS WITH SEVERE ACUTE PNEUMONIA

Case Number	Sex	Age (yrs)	FIo_2 %	Po_2 mm Hg	Pco_2 mm Hg	pH	So_2 %	$A\text{-}aDo_2$ mm Hg	Base Excess* mEq/litre	Lactate mM	Pyruvate mM	Lactate Pyruvate	SGPT S.F.	SGOT Units
1	F	0.2	98	212	90	7.17	100	376	+ 4.0	1.08	0.106	10.2	-	-
2	F	0.1	40	45	46	7.21	71	182	- 9.5	5.01	0.349	14.4	-	-
3	M	0.1	45	220	28	7.17	100	67	-18.3	14.25	0.536	26.6	-	-
4	M	1.0	40	125	52	7.31	98.1	96	+ 0.2	1.12	0.092	12.2	24	-
5	M	0.1	61	143	77	7.27	98.3	217	+ 7.4	1.35	0.076	17.7	57	64
6	F	0.3	21	71	30	7.40	94.6	41	- 6.0	2.04	0.079	25.8	21	48

* No prior infusion of sodium bicarbonate

TABLE 43

INITIAL MEASUREMENTS IN CHILDREN WITH ASTHMA BREATHING AIR

Case Number	Po_2 mm Hg	Pco_2 mm Hg	pH	So_2 %	$A\text{-}aDo_2$ mm Hg	Base Excess* mEq/litre	Lactate mM	Pyruvate mM	Lactate Pyruvate	SGPT S.F.	SGOT Units
1a	30	87	-	-	10	-	1.26	0.089	14.2	-	-
1b	65	39	7.36	92.0	30	- 3.5	1.19	-	-	-	-
1c	60	45	7.32	88.5	32	- 2.9	1.81	0.087	20.8	26	51
2	42	56	7.25	68.1	34	- 2.8	2.35	0.169	13.9	-	-
3	59	46	7.36	89.4	32	+ 0.2	0.69	0.092	7.5	-	-
4	61	45	7.43	91.8	28	+ 5.0	2.65	0.134	19.8	-	-
5	54	36	7.41	88.3	49	- 1.3	1.04	0.100	10.4	-	-
6	70	39	7.38	93.8	26	- 1.8	0.74	0.087	8.5	-	-
7	70	37	7.40	94.2	33	- 1.4	3.07	0.253	12.2	22	-
8	49	46	7.29	80.0	43	- 4.0	1.41	0.129	10.9	-	30
9	60	35	7.37	90.0	46	- 4.8	1.86	0.120	15.5	16	41
10	90	40	7.30	96.1	10	- 6.5	0.92	0.077	11.9	-	-
11	83	34	7.40	96.3	24	- 3.6	0.72	0.083	8.7	-	-
12a	85	38	7.36	96.0	18	- 5.0	1.92	0.185	10.4	-	-

* No prior alkali therapy.

TABLE 44

INITIAL MEASUREMENTS IN CHILDREN WITH CYSTIC FIBROSIS BREATHING AIR

Case Number +	Sex	Age (yrs)	Po_2 mm Hg	Pco_2 mm Hg	pH	So_2 %	$A\text{-}aDo_2$ mm Hg	Base Excess* mEq/litre	Lactate mM	Pyruvate mM	Lactate Pyruvate
1	F	0.2	50	54	7.38	84	32	+ 6.5	3.39	1.470	23.1
2	F	0.5	65	52	7.34	91	20	+ 2.6	1.32	0.082	16.1
3	M	3.0	68	39	7.40	94	33	- 0.5	1.55	0.134	11.6
4	M	0.5	64	52	7.38	92	21	+ 5.0	1.44	0.087	16.6
5	M	15.0	63	37	7.44	93	41	+ 1.0	0.916	0.077	11.9
6	F	0.6	77	40	7.40	95	23	0	1.64	0.126	13.0
7	F	0.9	90	37	7.38	97	14	- 2.9	1.12	0.083	13.5

* No prior infusion of sodium bicarbonate.

\+ Cases 1-4 studied during acute exacerbation of symptoms (Grade III).

TABLE 47

CHANGES IN BLOOD GAS TENSIONS, AND LACTATE AND PYRUVATE FOLLOWING THE ADMINISTRATION OF OXYGEN*

Case Number	FIo_2 %	Po_2 mm Hg	Pco_2 mm Hg	pH	Base Excess mEq/litre	Lactate mM	Pyruvate mM	Lactate Pyruvate	So_2 %	$A\text{-}aDo_2$ mm Hg	Cao_2 vols%
1	21	49	40	7.34	- 3.8	1.62	0.121	13.4	82	46	21.2
	80	80	45	7.34	- 1.5	0.90	0.071	12.7	95	417	24.6
2	21	41	44	7.38	+ 0.5	1.88	0.100	18.8	75	50	20.6
	76	54	44	7.39	+ 1.4	1.90	-	-	87	419	24.0
4	21	24	34	7.36	- 5.8	1.08	0.065	16.6	42	70.5	12.7
	95	35	34	7.40	- 3.2	1.18	-	-	68	589	20.5
7	21	33	41	7.35	- 2.8	1.78	0.177	10.1	61	64	16.4
	92	46	39	7.34	- 4.6	1.66	0.136	12.2	79	531	21.3
9	21	27	36	7.42	- 0.8	6.66	0.122	54.6	53	77	14.1
	100	31	33	7.39	- 4.7	1.18	0.089	13.3	60	625	16.0

* Time interval between samples is 25-30 minutes, except in Case 9 who was treated for 48 hours with 60-70% oxygen before the second sample was obtained.

TABLE 49

OXYGEN CONCENTRATIONS IN INCUBATORS

Incubator Model	Number of Observations	Oxygen Flow Rate (litres/min)	Actual Concentration at Child's Mouth (%)		Possible Oxygen Concentration Claimed (%)
			Range	Mean	
Intensive-Care Isolette (Air-Shields, Inc.)	3	1 (red handle horizontal)	26	26	
		2 "	30 - 30.5	30.3	
		3 "	34 - 35	34.5	28 - 30
		4 "	38 - 39	38.6	
		$4\frac{1}{2}$ "	40 - 44	43	32 - 35
		$4\frac{1}{2}$ (after 30 minutes with red handle vertical)	58 - 71	63	70+
New Incubator (Oxygenaire Ltd.)	1	1 (air intake open)		27	29
		2 "		34	34
		3 "		37	35
		6 "		35	35
		6 (after 30 minutes with red blanking disc in position)		63	80
Series III (Oxygenaire Ltd.)	5	1	24 - 29	27	25
		2	29 - 40	36	35
		3	35 - 45	41	45
Portable Incubator Mark III (Oxygenaire Ltd.)	1	2		25	Less than 30 unless special face mark is used.
		4		31	
		6		38	
		8		48	